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VITAMIN A ABSORPTION IN CATARRHAL JAUNDICE

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IN the course of studies on vitamin A absorption by patients with various illnesses, it became apparent that abnormal absorption of vitamin A occurred in diseases of the liver, as well as in the cases of celiac disease.[1]

This report is based upon a study of twenty-one patients with catarrhal jaundice admitted to the Pediatric Divisions of the Strong Memorial and Rochester Municipal Hospitals in the past eight years and upon whom vitamin A absorption tests were done.

The technique of the vitamin A absorption test has been reported previously.[2] In brief, after a basal blood is taken, a measured amount of high potency fish liver oil* is given to the patient by mouth, and blood samples are taken at intervals of 2, 4, 6, 9, 12, and 24 hours. These samples are analyzed for vitamin A by the method of Carr and Price modified by McCoord and Clausen.[3] In the patient whose absorption is normal, the maximum amount of vitamin A in the blood is found four hours after ingestion of the oil and averages 170 blue units† of vitamin A per 100 c.c. of blood.[1]

In most patients with catarrhal jaundice this normal absorption did not occur. The results of the tests, together with the pertinent clinical and laboratory data of all cases tested, are given in Table I. For the most part, these cases were typical of catarrhal jaundice. Symptoms, or signs, which were definitely recorded as present are tabulated as "Yes" in Table I; those which were either not mentioned or definitely said to be absent are tabulated as "No." It is probable, in some cases, that signs and symptoms which were present failed to be mentioned in the patient's record. In severity the cases varied from the mild (Case 4),

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*We wish to acknowledge the kindness of Dr. Carl Nielsen, of the Abbott Laboratories, who supplied us with the fish liver oil used in these tests.

†The "blue unit" of vitamin A is approximately equivalent to between 3.5 and 4.0 U.S.P. units.

TABLE I

	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5	CASE 6	CASE 7	CASE 8	CASE 9
Age	12	9	12	8	8	12	7	6	6
Sex	F	M	M	F	F	M	F	M	M
Abdominal pain	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Vomiting	Yes	Yes	No	No	Yes	No	Yes	Yes	No
Fever	Yes	No	No	Yes	Yes	No	Yes	No	Yes
Anorexia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Headache	No	No	Yes	Yes	No	Yes	Yes	No	Yes
Enlarged liver	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Enlarged spleen	Yes	No	No	No	No	No	No	No	No
Jaundice	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Clay stools	No	Yes	No	No	Yes	Yes	Yes	No	Yes
Dark urine	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Previous respiratory infection	No	No	No	Yes	No	Yes	Yes	No	No
Familial incidence	No	No	No	No	Yes	No	No	No	Yes
Day of jaundice on admission	7	5	--	1	1	4	1	1	1
Day of disease on admission	8	14	4	7	4	14	4	2	14
Total white blood cell count	--	9,100	13,150	22,400	8,400	5,400	10,300	5,900	7,900
Icteric index	20	80	24	32	64	44	40	24	20	24	10	56
Van den Bergh test (mg. %)	1.6	7.5	1.1	--	5.3	--	--	3	--	3	--	6.4
Bromsulphalein test (dye recovered in one hour)	--	--	--	--	--	--	--	--	20%	30%	0	--
Day of disease vitamin A test	10	16	6	9	17	--	10	17	7	16	2	11	16
Condition of patient	Improving	Improving	Improving	Improving	Well	--	Improving	Active	Active	Improving	Active	Well	Active
Fasting value	15	9	5	2	21	--	3	9	3	16	1	10	5
2 hours	45	100	8	4	201	--	6	14	12	56	9	16	30
4 hours	236	165	80	3	764	--	200	30	11	132	119	267	198
6 hours	183	88	172	5	1,174	--	500	576	39	104	119	266	109
9 hours	110	67	97	--	2,744	--	270	286	68	93	69	137	81
12 hours	85	23	50	--	--	--	--	116	36	54	48	118	76
24 hours	28	21	12	2	468	--	24	30	12	26	14	55	20
Total rise	221	156	167	3	2,723	--	497	567	65	116	118	257	193
Remarks													

TABLE I—CONT'D

	CASE 10	CASE 11	CASE 12	CASE 13	CASE 14	CASE 15	CASE 16
Age	10	9	11	9	12	9	5
Sex	M	M	F	M	F	M	M
Abdominal pain	Yes	Yes	Yes	Yes	No	Yes	Yes
Vomiting	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Fever	Yes	Yes	Yes	No	Yes	Yes	No
Anorexia	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Headache	No	Yes	Yes	Yes	No	No	Yes
Enlarged liver	No	Yes	Yes	Yes	No	No	Yes
Enlarged spleen	Yes	No	No	No	No	No	No
Jaundice	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Clay stools	No −	Yes +	Yes +	Yes +	No −	Yes +	Yes +
Dark urine	Yes	Yes	Yes	Yes	Yes	Yes	No
Previous respiratory infection	Yes	No	No	No	No	No	Yes
Familial incidence	No	No	Yes	Yes	No	Yes	No
Day of jaundice on admission	Developed in hospital	2(?)	2	7	2	5	1
Day of disease on admission	--	14	7	14	7	10	4
Total white blood cell count	7,400	8,200	6,300	6,700	7,000	15,000	17,300
Icteric index	48 20	32 12	16 60 64	64	48	112	11
Van den Bergh test (mg. %)	-- --	3 --	1.9 -- --	--	4.5	--	--
Bromsulphalein test (dye recovered in one hour)	100% 10%	100% 5%	-- -- --	--	-- —	--	--
Day of disease vitamin A test	5 13	15 25	-- 9 11	16 17	9 10 11	10	6
Condition of patient	Active Improving	Active Improving	-- Active Active	Active Active	Active Active Active	Active	Improving
Fasting value	6 5	5 15	-- 8 10	0 40	4 40 --	5	11
2 hours	10 7	5 23	-- 9 24	-- 36	19 -- --	--	--
4 hours	5 301	6 269	-- 55 445	2 42	90 229 248	--	233
6 hours	8 279	7 205	-- 43 322	-- 63	74 94 --	--	--
9 hours	7 169	11 175	-- 18 180	11 159	51 -- --	--	146
12 hours	7 72	10 91	-- -- --	-- 179	40 -- --	--	--
24 hours	10 31	12 41	-- -- --	40 42	-- -- --	--	32 (48 hr.)
Total rise	4 296	6 254	-- 47 435	40 119	86 189 208(?)	--	222
Remarks	Admitted for otitis media		-- No bile given Bile salts given	No bile given Bile salts given	No bile given Bile given No bile given	Died	

TABLE I—CONT'D

	CASE 17			CASE 18				CASE 19			CASE 20			CASE 21	
Age	9			10				12			14			12	
Sex	F			M				M			F			F	
Abdominal pain	Yes			Yes				Yes			Yes			No	
Vomiting	Yes			Yes				Yes			Yes			Yes	
Fever	Yes			Yes				Yes			Yes			Yes	
Anorexia	Yes			Yes				Yes			Yes			Yes	
Headache	Yes			No				No			No			Yes	
Enlarged liver	No			Yes				Yes			Yes			Yes	
Enlarged spleen	No			Yes				Yes			Yes			No	
Jaundice	Yes			Yes				Yes			Yes			Yes	
Clay stools	No —			Yes +				No —			Yes +			Yes +	
Dark urine	No			Yes				No			Yes			Yes	
Previous respiratory infection	No			No				Rheumatic fever			No			No	
Familial incidence	No			No				No			No			Yes	
Day of jaundice on admission	After admission			7				After admission			3			After admission	
Day of disease on admission	7			6th week (?)				After admission			7			4	
Total white blood cell count	7,500			5,000				--			7,900			5,000	
Icteric index	40			56	88	80	80	56	56		60	56		--	28
Van den Bergh test (mg. %)	--			5	--	--	--	--	--		--	--		3.7	--
Bromsulphalein test (dye recovered in one hour)	--			64% (½ hr.)	--	--	--	--	40%		--	--		--	--
Day of disease vitamin A test	2	3	5	9	11	13	14	3	4	5	9	10	11	9	15
Condition of patient	Active	Active	Active	Active	Active	Active	Active	Active	Active	Active	Active	Active	Active	Active	Improving
Fasting value	3	21	41	2	2	2	4	2	18	36	4	18	59	5	10
2 hours	--	--	--	--	--	--	--	29	--	--	--	--	--	6	31
4 hours	13	258	415	4	26	4	6	28	199	158	53	221	107	5	596
6 hours	--	--	--	2	--	--	--	--	--	--	--	--	--	10	468
9 hours	--	--	--	2	49	4	14	--	138	133	80	56	86	9	193
12 hours	37	226	246	--	--	--	--	29	--	--	--	--	--	--	114
24 hours	21	--	--	--	--	--	--	18	36	--	18	59	--	9	56
Total rise	34	237	374	2	47	2	10	27	181	122	76	203	48	5	586
Remarks	No bile given	Bile given	No bile given	No bile given	Bile given	No bile given	Saponified vitamin A given	No bile given	Bile given	No bile given	No bile given	Bile given	No bile given		

in which no clinical jaundice could be noted, to the fatal (Case 15), in which the patient was too ill to have a complete test done. In six of the twenty-one cases (5, 9, 12, 13, 15, and 21) there was a history of other cases of jaundice in the same family.

Although in six patients (Cases 1, 2, 3, 8, 9, and 16) the test showed normal curves, in the remaining children either vitamin A was absorbed poorly or the rise in the blood was found to be much higher than normal.

In all cases where the absorption was poor on the original test (Cases 4, 7, 10-14, and 17-21) later tests showed an increase in the ability to absorb vitamin A. We consider as normal a rise to between 100 and 350 blue units. Four of these patients (Cases 4, 12, 17, and 21) showed, on this basis, a peak absorption higher than this when retested, one case (18) lower than 100 units, and the others within the normal range. In Cases 5 and 6 the original test was higher than the above-mentioned standard.

Fourteen cases were tested within nine days of the onset of the disease. Ten of these fourteen cases (72 per cent) failed to absorb the vitamin well. Sixteen cases were either retested or had the original test ten days or more after the onset of the illness. Only three of these cases (19 per cent) failed to absorb at least a normal amount of vitamin A. Although the number of cases involved is small, this difference of 53 per cent between the two groups is probably of statistical significance.

If, instead of dividing the cases into two groups on the basis of length of illness only, we consider the patients from the clinical standpoint and try to classify them as improving or not improving on a basis of all available data, we find that, in the group where no improvement was taking place at the time of the test, eleven of fifteen cases (74 per cent) failed to absorb vitamin A well. But in only one of thirteen cases (8 per cent) did failure to absorb vitamin A occur when apparent clinical improvement was taking place. This difference of 66 per cent is also probably significant.

There was no apparent correlation between the degree of icterus in the group of cases as a whole and the vitamin A absorption test, although in individual patients improvement in the degree of icterus was associated with improvement in the ability to absorb vitamin A.

Eight bromsulphalein tests for liver function were done in six cases. In Cases 10 and 11 in which 100 per cent of the dye was recovered from the blood in one hour, and in Case 18 in which 64 per cent of the dye was recovered in one-half hour, denoting severe damage to liver function, little vitamin A was absorbed. Case 18 was not retested, but the first two cases were, and improvement in the bromsulphalein test was associated with improvement in the patient's ability to absorb vitamin A. In Cases 7, 8, and 19, in which the amount of dye retained in one hour was 20 per cent, 30 per cent, and 40 per cent, respectively (definitely pathologic levels), the absorption of vitamin A was nearly normal.

To seven patients (Cases 12, 13, 14, 17, 18, 19, and 20) upon whom vitamin A tests were done during the active stage of the disease and who showed failure to absorb the vitamin, bile salts were given within two days of the original test, and the tests were repeated.* In all of these cases improvement took place in absorption when the bile salts were given. A third test was done in five of the seven cases following this, but without giving bile salts. In three of these patients the rise of vitamin A in the blood was greater when the bile salts were given, but in two cases the subsequent test without the bile salts showed the higher rise in the blood vitamin A.

In summary, the results of these tests of vitamin A absorption in twenty-one cases of catarrhal jaundice showed:

1. The original test was normal in six cases.

2. The original test showed an unusually high rise in the vitamin A of the blood in two cases.

3. The original test showed failure of normal absorption in twelve cases. In these cases, when the test was repeated, (a) seven cases returned to normal levels; (b) four cases showed a rise of vitamin A above normal; (c) one case showed improvement but not normal absorption.

4. There was one fatal case in which only one determination of vitamin A was made. This value was low.

5. Ten of fourteen cases tested within nine days of onset of the disease failed to absorb vitamin A well, whereas, only three of sixteen cases tested at least ten days or more after the onset failed to absorb vitamin A well.

6. Eleven of fifteen cases who were tested, while not improving from a clinical standpoint, failed to absorb vitamin A well, whereas, only one of thirteen cases tested while improving failed to absorb at least a normal amount of vitamin A.

7. The height of icterus as measured by the icteric index did not bear any obvious correlation to vitamin A absorption.

8. Severe degrees of liver damage as measured by bromsulphalein test were associated in three cases with failure to absorb vitamin A, whereas lesser degrees of damage were not.

9. Patients with low curves who were given bile salts and retested showed improvement in absorption. In most cases, however, this improvement was maintained when the test was repeated again without the use of bile salts.

DISCUSSION

Since vitamin A is fat-soluble, bile should be necessary for its absorption. Since in most cases of catarrhal jaundice the bile excretion into the intestine is diminished, failure of absorption of vitamin A might be expected to occur in this disease.

This failure of absorption occurred in most of our cases.

*The bile salts, or sodium taurocholate, used were obtained from the McNeil Laboratories. Each child received approximately 1 gm. for each 30 kg. of body weight.

Normal curves occurring in the disease might be due to one of two causes. First, mild cases may show no failure of absorption. Second, the cases were recovering when the test was first done. We feel that the latter explanation is the more correct.

The variation in the recovery time in the disease may explain why some cases absorbed normally within ten days, and in other cases, abnormal absorption still occurred after ten days.

Accurate determination of improvement from clinical data alone also presents difficulties, so that some cases which we felt were active or getting worse were actually improving and vice versa. This may explain the lack of complete correlation between our vitamin A tests and the clinical impression.

The explanation of the unusually high levels of blood vitamin A reached in some of the cases, particularly Case 4, is not clear. Possibly more bile is excreted suddenly in the recovery stage, making absorption easier. Another explanation may be that the liver is capable of forming bile relatively early in the recovery stage, but is not capable of removing vitamin A from the blood, thus giving rise to the high levels encountered.

Some correlation between liver function tests and vitamin A absorption might be expected and seems to exist in the few patients tested by the bromsulphalein test.

If lack of bile salts is the explanation for failure of vitamin A absorption in catarrhal jaundice, the addition of these salts in adequate amounts should improve the absorption of vitamin A. In our cases this seemed to be true. However, this conclusion is not absolutely established by our data because there was no way of definitely knowing whether the improvement was due to the natural course of recovery in the disease or due to the bile salts that were given to the patients.

CONCLUSIONS

In cases of catarrhal jaundice in the active stage, vitamin A is usually poorly absorbed when given by mouth.

With improvement in the disease, the rise in vitamin A in the blood after ingestion is equal to, or higher than, that of the normal person.

Bile salts probably aid in the absorption of vitamin A when given by mouth to patients with catarrhal jaundice.

We wish to acknowledge the valuable suggestions and help given us by Dr. S. W. Clausen. He first suggested the use of bile salts in these patients, and it is his modification of the Price-Carr method of determining vitamin A which was used throughout the work. We also wish to thank the many house officers on the pediatric service for their help and cooperation in obtaining the blood specimens in these patients.

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THE BASAL METABOLISM OF OBESE CHILDREN

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IN earlier papers[1-3] an attempt has been made to clarify the meaning of basal metabolism measurements in children of unusual body build by estimating the rate of heat production of the active protoplasmic mass. The present paper is an extension of this work and reports measurements on obese children. The evidence presented suggests that ordinary obese children are not suffering from a glandular deficiency.

From the point of view of energy metabolism, the body is composed of two types of tissues—those which produce heat and those which presumably do not. These are spoken of as "active" and "inactive" tissues, respectively. The body musculature forms a major and relatively constant part of the active tissue mass, whereas bone, fat, and water are examples of the inactive types. Attention has been focused on the active tissues because of the belief that they are the chief source of body heat. If this theory* is correct, then it is important for an understanding of the metabolism of obese children to know at what rate these particular tissues are producing heat, because they are presumably the tissues upon which the various stimuli which tend to raise and lower the metabolism act.

An answer to this question necessitates the division of total body tissue into "active" and "inactive" tissue. The "active" mass can be measured by determining the creatinine output in the urine per twenty-four hours.[1, 9] Determination of the creatinine coefficient (Table I) (i.e., creatinine output in milligrams divided by weight in kilograms) in obese children† shows it to be 40 per cent lower than in normal children‡ (Table II).[9] This means that the fat child has 40 per cent less heat-producing tissue per kilogram of body weight than the normal child. The obese child has, however, an approximately normal amount of musculature for his height. This is evidenced by the fact that the creatinine-height coefficient (i.e., milligrams creatinine per twenty-four

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*This theory was first offered by Voit.[4] It has been discussed subsequently by Harris and Benedict,[5] Topper and Muller,[6] Talbot,[7] Du Bois,[8] and others.

†For the purposes of this discussion measurements of the basal heat production, creatinine output, and skeletal age have been measured upon a group of typical fat children. These children presented no evidence of endocrine disorder unless obesity per se is considered evidence. The procedures employed for the collection of metabolic data are described elsewhere.[1-3, 9] The skeletal age was estimated from roentgenograms of the wrist by referring to Todd's normal standards. We are indebted to Dr. E. C. Vogt and Dr. G. Wyatt for these estimations and to Mrs. J. Dingle and Miss Morse for their assistance in obtaining the metabolism data.

‡The values reported in Table II were calculated from data collected on normal school children.[9]

TABLE I

OBSERVATIONS ON OBESE CHILDREN

PATIENT	AGE	SEX	MG. CREATININE PER KG.	MG. CREATININE PER CM.	BASAL METABOLIC RATE (PERCENTAGE)			HEIGHT COMPARED TO AVERAGE HEIGHT FOR AGE* (INCHES)	SKELETAL AGE COMPARED TO AVERAGE FOR AGE† (YEARS)
					CREATININE STANDARD	WEIGHT STANDARD	HEIGHT STANDARD		
M. R.	10 7/12	F	8.1		+31	−14	+15	+4½	
C. S.	7 1/12	F	14.6	4.8	+16	− 1	+18	+6	
M. R.	9 5/12	F	13.9	4.7	+ 1	−12	+ 9	+4	
B. A.	8 1/12	F	15.0	5.0	+ 5	− 7	+11	+6	
E. B.	11 4/12	F	12.1	4.3	+ 4	−19	− 1	0	
C. S.	8 10/12	F	8.0	4.5	+31	− 4	+50	+3	+1
M. M.	11 4/12	F	10.0	3.5	+35	0	+ 9	+5	
H. F.	9 10/12	F	12.8	4.6	+13	− 6	+19	+2	
L. S.	11 9/12	F	8.6	3.9	+ 9	−21	+ 5	−1	− ½
C. B.	5 9/12	F	9.7	2.5	+ 4	− 8	+14	0	
A. S.	11 11/12	F	15.8	8.7	+ 6	− 9	+18	+6	
J. G.	7 9/12	F				− 8	+17	+6	0
A. W.	8	F	8.0	2.6	+21	− 8	+17	+3½	+2
V. S.	7 3/12	F			+11	+ 7	+40	+5½	+1
B. H.	6	F	13.6	3.5	+ 5	0	+22	+4	+ ½
G. S.	9 4/12	F	8.0	2.6	+37	+ 5	+28	+2	0
E. K.	8 9/12	F	15.0	4.4	0	− 2	+24	+1	0
H. C.	8	F	16.0	4.1	+ 9	+ 5	+25	+2	0
R. Q.	10	F	16.0	5.2	+15	+ 2	+25	+1	
L. C.	11 9/12	F							− ¾
D. N.	6 11/12	F	12.5		+15	− 2	+30	+5½	+4½
F. S.	5 8/12	M				+ 9	+45	+4½	+3
C. M.	10 4/12	M				+ 6	+41	+3	0
H. S.	10 11/12	M	16.0	5.6	+14	− 5	+17	+1	
G. N.	9	M						+3	+1
M. C.	8 3/12	M							+1¼
Average			12.3	4.4	+14.1	− 4.1	+21.7	+3.3	+0.9

*Baldwin-Wood Tables.

†Todd Standards. Normal range ±2 years.

hours divided by height in centimeters) is approximately the same for the obese (Table I) and normal (Table II) subjects. Thus, it would appear that the chief difference between the normal and the adipose person is that the latter has accumulated an abnormal amount of adipose tissue. This abnormality of obese children must be considered in any study of the energy metabolism of these children.

TABLE II

AVERAGE VALUES FOR NORMAL CHILDREN FROM 6 TO 14 YEARS OF AGE

	MALES	FEMALES
Mg. creatinine per kg. of weight		
Average	21.99	19.42
Standard deviation	3.1	2.9
Mg. creatinine per cm. of height		
Average		5.03
Standard deviation		1.1

Several standards of metabolism are available. They serve the purpose of a common denominator by which the basal heat production of a person may be compared with that of a group of normal persons. The creatinine standard[2, 3] enables the clinician to estimate the basal metabolic rate* of the heat-producing tissues, and the weight standard,[10] that of the total body mass. The height standard[10] differs fundamentally from the former two because height is a measure of stature rather than mass. Therefore, when the heat production is referred to the height standard, it will have significance only in so far as height is proportional to total body mass or protoplasmic mass.

With this information as a background, it is relatively easy to understand the various metabolic rates observed in obese children (Table I). The average rate obtained by referring to the creatinine standard is +14 per cent. This seems to indicate that the active protoplasmic mass is producing heat at an accelerated rate in these children. The height standard gives results (average +22 per cent) comparable to those obtained from the creatinine standard. It is probable that this is so chiefly because the ratio of the active protoplasm to the height has not changed. This relationship is not sufficiently reliable, however, to permit the substitution of the height for the creatinine measurement in individual patients. An average metabolic rate of −4.1 per cent is observed when total calories are referred to the weight standard. This is taken to mean that these children were producing slightly less than the average amount of heat for their total mass. Apparently the heat-producing tissues had been stimulated to produce more heat, in order that the energy requirements of the body as a whole (represented by weight) might be met.

*The metabolic rate is determined by finding the percentage difference, plus or minus, between the total calories produced by the patient and the total calories which a standard predicts he should produce, relative to his creatinine output, weight, height, or body surface. The body surface standard has not been used in this discussion because the available evidence[7] indicates that body surface cannot be measured accurately from the height and weight of obese children.

Although it is not clear just where this stimulus comes from, certain possibilities may be considered. It is well known that some of the endocrine glands influence the metabolism. Means[11] and Cushing and Davidoff[12] have shown that deficiency of either thyroid or anterior pituitary results in a lowered heat production. Likewise, it is well recognized that the metabolic rate is elevated in hyperthyroidism.[8, 11] There are, however, many accessory factors which may modify the amount of heat produced even under basal conditions. Talbot, Wilson, and Worcester[7] report that, when a child is growing rapidly, at no matter what the age, the metabolism is higher than that of a more slowly growing child. Du Bois[8] and Talbot et al.[7] discuss at length the possible influence of nutrition on the production of heat. They also shown that the state of puberty may be characterized by an elevated heat production. For these reasons caution should be used in interpreting the apparently elevated metabolic rate of the protoplasmic mass to mean that a state of hyperthyroidism existed, although it is possible that the stimulus is mediated through one or more of the endocrine glands.

The foregoing findings taken together seem to indicate that in obesity the metabolism is either normal or moderately elevated. This fits in with other clinical observations made upon these children. Their height (Table I), for example, averaged 3 inches above the mean height of normal children of the same age, although it was within the upper limits of normal in every instance. Furthermore, their skeletal age (Table I) was found to be either average normal or slightly advanced. Evans[13] has shown that, in the absence of the anterior pituitary gland, there is immediate cessation of growth and development in young animals. Cushing[14] describes patients who were dwarfed and immature as a consequence of proved pituitary disease. Stunting of growth is a striking characteristic of thyroid deficiency during childhood.[11] Another sensitive index of juvenile hypothyroidism is the retardation of skeletal age first noted by Her Toghe[15] and subsequently confirmed by many observers.[16] Because the obese children reported here were taller than average and had, if anything, slightly advanced skeletal development, it seems logical to conclude that they were not suffering from anterior pituitary or thyroid deficiency. Bruch[17] came to the same conclusion after making observations on the stature and skeletal and sexual development of a similar group of adipose children. Viewed as a whole, the available evidence suggests, therefore, that the clinician need not worry that children similar to those reported here are suffering from a deficiency of anterior pituitary or thyroid products.

The elevated metabolic rate indicated by the creatinine standard appears to fit the total clinical picture better than the lowered rate suggested by the weight standard. This leads us to persist in our earlier tentative conclusion that the creatinine standard of metabolism gives a truer picture of the energy metabolism than other standards which do not take the active protoplasmic mass into account.

SUMMARY AND CONCLUSIONS

Previous work on the relationship between basal energy metabolism and the active protoplasmic mass (as measured by creatinine) in average normal children has been extended to include obese children. The data obtained indicate that the basal metabolic rate of the protoplasmic mass is moderately elevated in adipose children. This finding, supplemented by measurements of stature and skeletal maturation, signifies that fat boys and girls similar to the constitutional type described here are not necessarily suffering from a deficiency of anterior pituitary or thyroid hormones.

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SERIAL BLOOD SUGAR DETERMINATIONS IN NORMAL NEWBORN INFANTS

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THE inadequacy of existing information concerning the blood sugar values of normal newborn infants and the recent interest expressed in their carbohydrate metabolism[1-9] furnish the rationale of this report. The statistics are based on 1,586 blood sugar determinations made upon seventy-three normal newborn infants and upon one infant of a diabetic mother.

PLAN OF STUDY

It was purposed to obtain data illustrating the normal trend of the blood sugar during the first two weeks of life. Clinic inpatients of the Boston Lying-in Hospital were used in this study.

During the time that any infant was included in the study, its blood sugar was determined at intervals of eight hours. Each blood sample was collected at least three and one-half hours postprandial. The babies were studied in two groups. The first group dealt with thirty-four infants, each followed for a period of about seven days starting at birth. The second group was concerned with older infants, followed usually to the termination of the hospital stay of two weeks. Newborn infants were first fed at the regular feeding period which most nearly coincided with the end of their first 24-hour period. After this, they were gradually put onto a regular four-hour schedule.

Only babies exhibiting a normal course during their hospital stay are included in the statistics. A temperature elevation which did not respond immediately to sterile water by mouth excluded the infant from the normal group.

TECHNICAL PROCEDURE

The micromethod of Folin,[9] as described in his last paper on this subject, was used. The method was modified* to simplify the preparation of the necessary solutions.

From the Departments of Pediatrics and Obstetrics, Harvard Medical School, and the Boston Lying-in Hospital.

*I am indebted to Miss Hazel Hunt, Director of the Clinical Laboratory of the New England Deaconess Hospital, for the following suggestions as to technical procedure.

Reagent number 1 (sulfate-tungstate solution) and reagent number 2 (sulphuric acid) of the *New England Journal of Medicine*[10] method of Folin are combined into one solution: Dilute tungstic acid solution. This is freshly made each day as follows: In a 250 c.c. volumetric flask place approximately 100 c.c. of distilled water. Add 5 c.c. of 10 per cent sodium tungstate and 5 c.c. of ⅔ N sulphuric acid. Dilute to volume with distilled water and mix.

In the determination 10 c.c. of this dilute tungstic acid solution are used in place of 4 c.c. of reagent number 1 plus 1 c.c. of reagent number 2. In keeping with this, 4 c.c. of the clear supernatant fluid are used for each determination in place of 2 c.c. as described in Folin's paper. This procedure is the one followed at the New England Deaconess Hospital in the clinic of Dr. Elliott P. Joslin.

The value obtained is the "total reducing substance" of the blood and not the "true blood sugar."[10, 14] The standard glucose solution was checked at intervals by the clinical laboratories of the New England Deaconess Hospital and the Children's and Infants' Hospital of Boston. All samples were collected and calculated by the writer. Calculation was done immediately to minimize error due to glycolysis.

PRESENTATION OF DATA

Charts 1 and 2 give the trend of the blood sugar values found during the first two weeks of life in the seventy-four normal infants studied. Tables I and II give the figures from which Charts 1 and 2 were constructed. The middle line on each chart shows the average figure; the upper line is the highest individual value obtained, and the lower line indicates the lowest value found for each 24-hour period.

The average trend during the first three 24-hour periods is downward. From the third 24-hour period to the eighth 24-hour period the trend is gradually upward. During the second week of life the average is seen to remain between 80 mg. per cent and 90 mg. per cent. The low extreme values are seen to ascend gradually from birth and during the last six 24-hour periods lie above 60 mg. per cent. The high extreme values show a less clear-cut alteration, but during the last week all fall below 120 mg.

TABLE I

DATA FOR FEMALES (CHART 1)

	24-HOUR PERIODS													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Maximum	160	109	99	99	111	120	105	114	110	100	118	105	114	100
Average	82	77	73	78	79	79	81	85	86	85	85	89	85	84
Minimum	55	59	54	52	54	43	54	67	62	65	58	63	62	70
Number of determinations	65	46	46	52	63	81	93	56	58	42	43	35	34	15
Number of infants	16	16	16	18	23	29	33	22	26	17	21	13	19	9

TABLE II

DATA FOR MALES (CHART 2)

	24-HOUR PERIODS													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Maximum	113	102	93	109	109	111	110	109	113	109	105	109	103	99
Average	76	72	67	74	77	81	83	83	87	87	85	86	86	91
Minimum	45	45	45	43	53	56	54	55	66	67	59	69	68	83
Number of determinations	71	55	54	57	76	92	104	66	68	54	50	43	42	13
Number of infants	18	18	18	22	27	34	36	25	29	19	24	16	22	7

per cent. During the first four 24-hour periods, values for the male infants in this group (Chart 2) are appreciably lower than corresponding values for the female infants.

Charts 3, 4, 5, and 6 are examples of the various types of individual charts obtained.

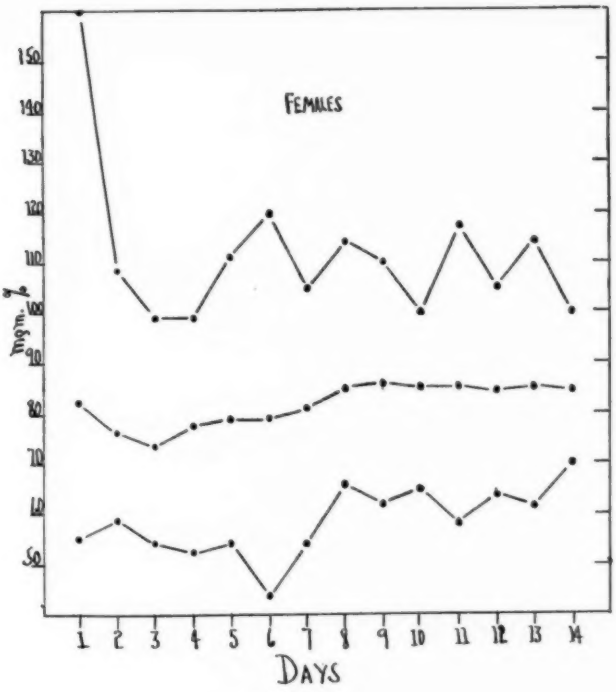


Chart 1.

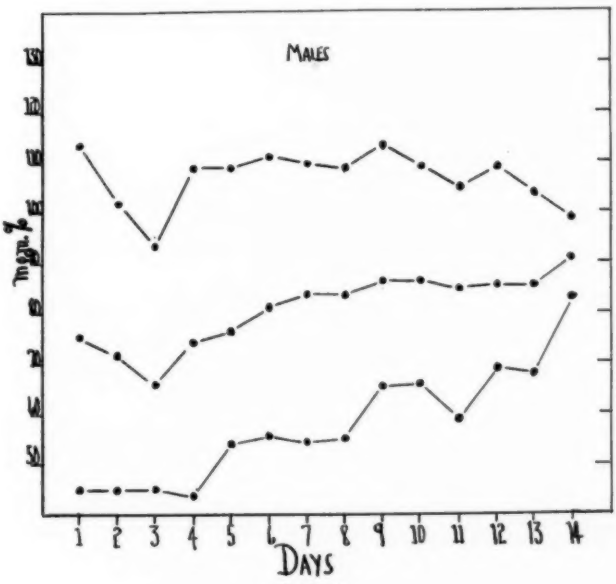
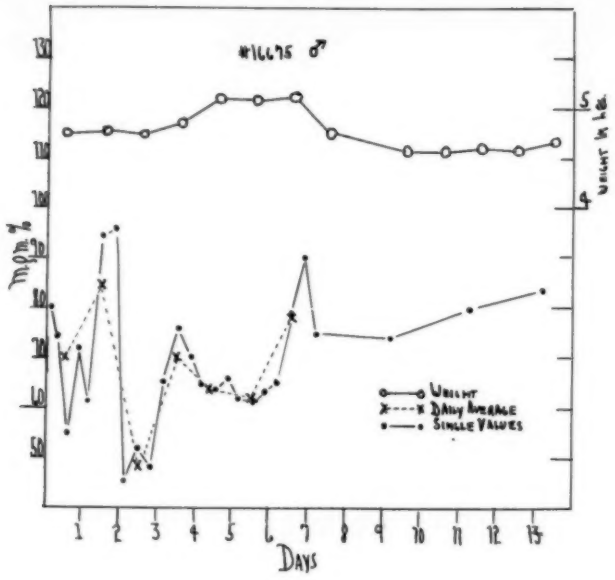
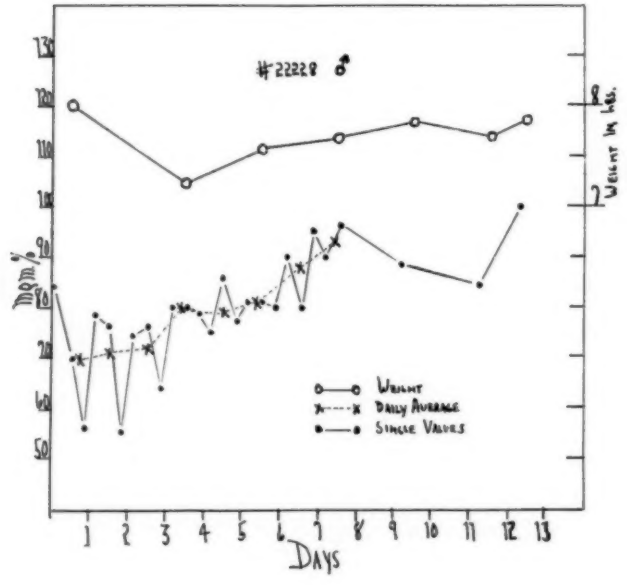


Chart 2.



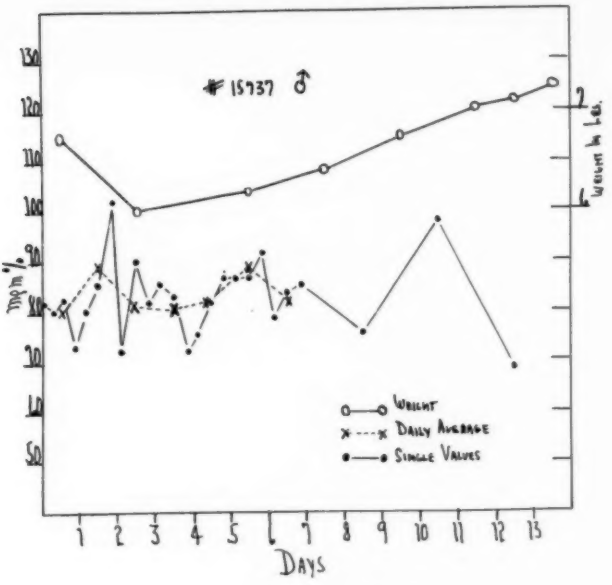
First Fed At 12 Hours

Chart 3.



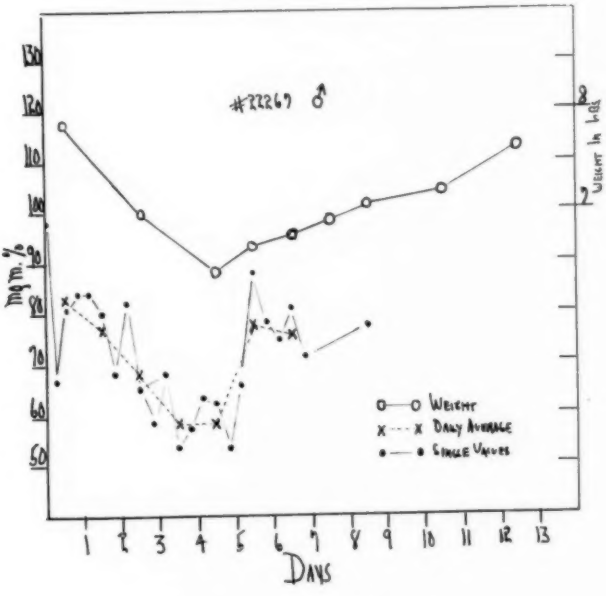
First Fed At 32 Hours

Chart 4.



First Fed At 37 Hours

Chart 5.



First Fed At 24 Hours

Chart 6.

TABLE III

NUMERICAL DISTRIBUTION OF BLOOD SUGAR VALUES FOR FEMALES

MG. %	DAYS													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
40-44.9	--	--	--	--	--	1	--	--	--	--	--	--	--	--
45-49.9	--	--	--	--	--	--	--	--	--	--	--	--	--	--
50-54.9	--	--	2	1	1	1	1	--	--	--	--	--	--	--
55-59.9	1	1	2	2	2	1	2	--	--	--	1	--	--	--
60-64.9	3	2	--	1	1	6	4	--	1	--	--	1	1	--
65-69.9	4	7	10	4	6	5	5	2	4	1	2	--	1	--
70-74.9	8	7	8	7	12	11	8	3	2	1	2	2	--	3
75-79.9	9	8	13	9	11	16	17	8	6	5	6	8	8	1
80-84.9	18	11	6	14	10	15	18	15	17	16	10	9	10	2
85-89.9	8	3	2	6	11	11	16	11	10	8	9	5	6	5
90-94.9	5	4	1	4	4	6	13	9	5	4	4	7	3	1
95-99.9	2	1	2	4	4	6	7	5	7	5	7	1	2	2
100-104.9	2	1	--	--	--	1	1	1	4	2	1	1	2	1
105-109.9	--	1	--	--	--	--	1	1	1	--	--	1	--	--
110-114.9	3	--	--	--	1	--	--	1	1	--	--	--	1	--
115-119.9	--	--	--	--	--	--	--	--	--	--	1	--	--	--
120-124.9	1	--	--	--	--	1	--	--	--	--	--	--	--	--
125-129.9	1	--	--	--	--	--	--	--	--	--	--	--	--	--
Totals	*65	46	46	52	63	81	93	56	58	42	43	35	34	15

*Single value of 160 Mg. per cent not included in table.

TABLE IV

NUMERICAL DISTRIBUTION OF BLOOD SUGAR VALUES FOR MALES

MG. %	DAYS													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
40-44.9	--	--	--	2	--	--	--	--	--	--	--	--	--	--
45-49.9	1	2	4	--	--	--	--	--	--	--	--	--	--	--
50-54.9	--	2	5	3	1	--	1	--	--	--	--	--	--	--
55-59.9	5	3	4	3	2	2	2	2	--	--	1	--	--	--
60-64.9	6	6	9	6	7	7	2	--	--	--	--	--	--	--
65-69.9	15	11	7	7	10	8	5	2	2	2	1	1	2	--
70-74.9	12	9	13	9	10	8	9	11	5	3	4	4	2	--
75-79.9	6	12	5	9	16	18	32	11	13	8	6	4	3	--
80-84.9	17	4	5	7	13	21	16	14	12	10	14	12	13	2
85-89.9	1	3	--	6	12	16	14	10	9	12	12	8	9	4
90-94.9	1	1	2	1	2	5	11	9	14	12	8	10	9	4
95-99.9	2	1	--	2	1	5	5	6	10	4	2	1	2	3
100-104.9	2	1	--	1	1	--	4	1	2	1	1	1	2	--
105-109.9	2	--	--	1	1	1	2	--	--	2	1	1	--	--
110-114.9	1	--	--	--	--	1	1	--	1	--	--	1	--	--
115-119.9	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Totals	71	55	54	57	76	92	104	66	68	54	50	43	42	13

Dr. Frederick C. Irving of the Department of Obstetrics of the Harvard Medical School has granted permission to report the serial blood sugar values obtained from the infant of a mild diabetic mother delivered by him. These values are shown on Chart 7. This infant was first fed twenty-four hours after birth, having received no oral or parenteral feedings before that time. Feedings were at four-hour intervals, and the blood samples were taken just before the succeeding feeding. At no time were extra additions made to the carbohydrate intake. The course followed by this infant is not dissimilar from that of the normal infants studied. The mother's diabetes was first detected during pregnancy and was well under control throughout gestation.

Table V gives comparative maternal and fetal blood sugar values obtained at birth. Determinations were made upon sixteen male infants and fifteen mothers (one pair of twins) and upon thirteen female infants and mothers. All maternal values were collected within twenty minutes of birth, the great majority within ten minutes of delivery. Most of the mothers received small amounts of ether during the second stage of labor.

TABLE V

AVERAGE MATERNAL AND FETAL CAPILLARY BLOOD SUGAR VALUES AT BIRTH

	FETAL	MATERNAL
Males	72 mg. %	105 mg. %
Females	92 mg. %	109 mg. %

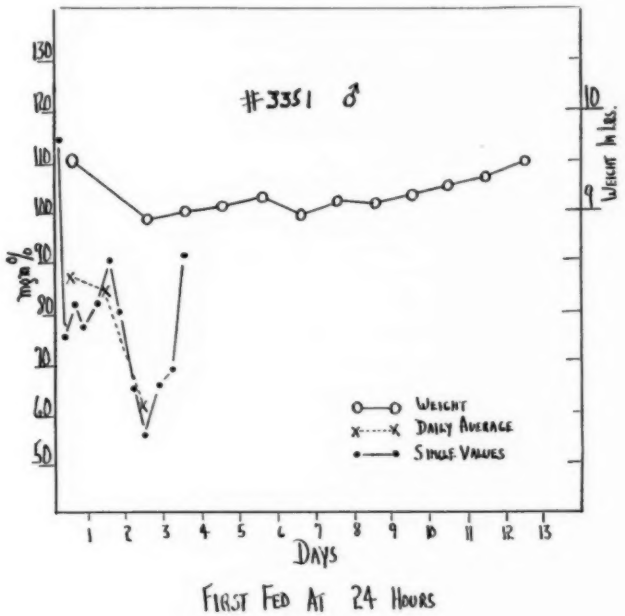


Chart 7.

The percentage difference between the average maternal and the average fetal values is 31.2 mg. per cent in the male infant group and 15.6 mg. per cent in the female infant group. This marked difference is due to the lower average value obtained in the male infant group since the maternal average in each instance is essentially similar.

REVIEW OF LITERATURE

A complete review of the literature on blood sugar values in normal infants will not be made. It was known that the blood sugar values of infants may be expected to be lower than those of older children or

adults.[4, 7, 8, 11, 12] It was also known that there is a gradual rise in the premature infant's and the normal infant's blood sugar during the first few weeks of life.[7] Our findings are in agreement with these statements.

Von Creveld[7] studied premature infants and found low values for blood sugar early in life. He reports some values below 30 mg. per cent without abnormal phenomena being observed. He used the micromethod of Hagedorn and Jensen[13] which determines "total reducing substance" of the blood.

Of interest is a paper by Köhler[9] who made 479 "double determinations" on forty normal newborn children. She used the Herold modification of the Bang method of determining the blood sugar. This method determines "total reducing substances." Samples were never collected less than five and one-half hours after the preceding meal, and most of them were taken seven hours postprandial. One blood sugar value was obtained from each infant each day. She found the blood sugar lowest on the third day, with values going as low as 20 mg. per cent. At no time were symptoms observed to accompany these extremely low blood sugars. Köhler quotes M. Aldo as finding the low average blood sugar on the second day. Köhler feels that the weight curve is intimately associated with the blood sugar curve in that the weight drop is paralleled by the blood sugar drop. She divides normal infants into several groups on the basis of the rapidity with which the weight and blood sugar fall. Blood sugar is said to begin usually to rise two days before the weight. The heavier children presented the more rapid fall in weight and blood sugar. The more premature the infant, the less the fall in blood sugar and weight. Köhler finds 60 mg. per cent the average blood sugar value for the first day of life with variations from 92 mg. per cent to 34 mg. per cent. On the second and third day values as low as 20 mg. per cent were obtained.

STABILITY OF THE NEWBORN INFANT'S BLOOD SUGAR

Examination of the charts as a group reveals that there is considerable instability of the blood sugar in these infants. In the course of a few hours values may be found to vary greatly. This observation is very important for two reasons: One, it suggests an unstable blood sugar regulating apparatus in the newborn; and, two, a single determination of the blood sugar is apt to be misleading. In evaluating the examples of hypoglycemia, this tendency of the normal newborn infant's blood sugar level to vary greatly over a period of a few hours must not be overlooked. In the cases as reported,[1, 2, 3, 5, 6] frequent serial blood sugar determinations were not made. In the event that a given value is found to be low, there is no assurance that a sample taken a few hours hence may not be several points higher, even in the absence of intervening feedings. By the same reasoning, a value found high now may in a few hours be low. Therefore, in order to discover more accurately what a given infant's

blood sugar may be, it is necessary to make a series of determinations rather than just a single determination.

Examination of Charts 1 and 2 would seem to indicate progressive increase in stability of the blood sugar during the first two weeks of life. In this short time, the blood sugar is seen to reach a more stable level as shown by the diminution in the degree of spread of values during the second, as opposed to the first, week.

SUMMARY AND CONCLUSIONS

In summary it may be said that, during the first week of life, low blood sugar values may be expected and that the lowest point is reached by the average baby on the third day. On the basis of our figures, values above 40 mg. per cent blood sugar may be regarded as normal in the first week of life. During the second week the range is from 60 mg. per cent to 120 mg. per cent, with the average between 80 mg. per cent and 90 mg. per cent. The male infants studied were observed to run slightly lower values than the female infants in the first six 24-hour periods. During the first two weeks of life, there is a gradual elevation of the blood sugar values with a decrease in the spread of the maximum and minimum extremes.

The blood sugar regulating mechanism of the newborn infant is unstable and undergoes an alteration toward greater stability during the first two weeks of life.

Attention is called to the inaccuracy of conclusions based upon single determinations of the blood sugar in newborn infants and to the caution which should be employed in ascribing symptoms or death to hypoglycemia during the first week of life.

I should like to acknowledge the helpful interest shown me by Dr. Clement Smith of the Department of Pediatrics of the Harvard Medical School in organizing this work.

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INCIDENCE OF SKIN ERUPTIONS AMONG INFANTS AND PRESCHOOL CHILDREN

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IT IS well known that skin ailments constitute a large percentage of general and pediatric practice. Davison[1] states that skin diseases constitute 13 per cent of private and 16.5 per cent of hospital pediatric practice. Next to respiratory infection, skin eruptions among infants and children are probably the most common complaints of mothers. The skin clinics usually observe only children with well-marked skin complaints. The small nevi, scattered patches of eczema, fleeting urticarial eruptions, and many cases of dermatitis are probably seldom referred to the clinics for consultation and treatment. Occasionally, the mother may experiment with the child's diet, often eliminating or withholding essential food products, such as cod-liver oil, eggs, fruits, fruit juices, or cereals, all of which are needed for the proper development of the child.

Because of the great number of children observed at the child health stations, we felt that a study of the skin eruptions seen during the first years of life would be of general interest. Those who direct the health, growth, and progress of these children have the opportunity to observe them at regular intervals, to watch their development, and to note any change in their skins. Close observation would also afford an opportunity to observe any possible relationship between diet and skin eruptions. Such close and regular study should aid in establishing rules for the care of the skin, so as to minimize the hazards of skin eruption.

The material for our study was obtained from two baby health stations in New York City. The babies were first brought to these stations at the age of 3 or 4 weeks for examination, feeding, and observation. No medical or surgical treatment was given. When any abnormality was discovered, the mother was urged to take the infant to her private doctor or to a hospital clinic. The infants were brought in for consultation and advice nine or ten times during the first year and about four times during the second year. In addition, nurse conference days were held, when the babies were weighed and the mother consulted with the nurse. The babies registered at these stations were representative of metropolitan New York City. All races and nationalities were included. The education of the mothers differed greatly. Some of the mothers stayed at home to care for the babies, while others were compelled to work and the babies were brought to the station by a relative or guardian.

From the Department of Health, City of New York.

The study was conducted over a period of nine months. Only those children were included who attended regularly and kept their appointments. When any skin abnormality was observed, its extent, duration, and possible diagnosis were noted. If no medication was needed, that was explained to the mother. If medication was indicated, the mother was directed to her physician, or in case of indigency, to a hospital clinic. At subsequent visits, the progress of the skin eruption, whether or not it was under outside medical supervision, was observed and noted. The effects of change in diet and other relevant factors were observed and considered. In this manner, we believe that we obtained a composite picture of skin eruptions as observed in a large group of children taken from a cross section of our population in the lower income brackets.

TABLE I

AGE	NUMBER OF CASES OBSERVED	NUMBER SHOWING SKIN ERUPTION	PERCENTAGE
Under 1 yr.	825	246	29.9
1-2 yr.	650	68	10.4
2-6 yr.	221	35	11.0
Total	1,696	349	21.1

Colored children, 306 (18 per cent).
Skin eruptions among colored children, 16 per cent.

TABLE II

ERUPTIONS OBSERVED	NUMBER OF PATIENTS		
	UNDER 1 YR.	1-2 YR.	2-6 YR.
Infantile eczema	48	27	12
Folliculitis with dermatitis of face	57	4	0
Nevi, including hemangioma	28	3	5
Seborrheic eczema	38	5	3
Impetigo	38	9	2
Miliaria	14	7	2
Sunburn	2	0	1
Papular urticaria with eczema	9	9	3
Insect bites	5	3	3
Miscellaneous	7	1	4

ANALYSIS OF DATA

The tables represent our findings in graphic form. It is to be noted that we observed and studied 1,696 infants and preschool children, of whom 54 per cent were female and 46 per cent male. Of these, there were 825 under 1 year of age, 650 between the ages of 1 and 2 years, and 221 between 2 and 6 years of age. Among these, we found 349 who had some form of skin ailment. Some of these skin complaints were of fleeting nature, such as miliaria, gluteal dermatitis, papular urticaria, or intertriginous eruptions, while others were of a more permanent nature, such as the various forms of nevi, verrucae, or seborrheic and infantile eczemas. Among the 825 babies under 1 year of age, 246 (29.9 per cent) showed skin eruptions. Among the 650 between 1 and 2

years of age, 68 (10.4 per cent) had some form of skin trouble; while among the third group, 35 (11 per cent) of the 221 had an eruption. Among the 1,696 patients studied, 18 per cent were negro babies. The percentage of skin diseases among the negro group was appreciably lower than that among the white group.

There were thirty-five different diagnoses of skin eruptions encountered. It was decided that, for study purposes, these could be condensed and classified into ten major groups of eruptions. Thus the various nevi were grouped together, although the hemangioma type far outnumbered all others. All pyodermas, including the paronychial infections, were placed in one group. Among others, we had two cases of molluscum contagiosum, and one case each of herpes zoster, geographic tongue, and urticaria pigmentosa. Dixon[2] reported a study of 1,097 new cases of skin diseases among children. The analysis of his data does not permit comparison with our findings, for he fails to state the ages of his patients. From the large number of cases of acne vulgaris and scabies encountered by him, one would judge that his study was made among older children.

DISCUSSION AND COMMENT

Skin eruptions in infants and preschool children may be of endogenous origin or due to exogenous factors. Among the endogenous factors may be improper food, inability of the body to metabolize and utilize the ingested food, constipation, anemia, and allergy. In addition, we must recognize those unknown factors which are responsible for a host of skin eruptions, the causes of which still remain unknown. The exogenous factors are more easily understood and are generally important, for much can be accomplished in eliminating them as causes of skin eruptions. The infant's skin, which is very delicate, is exposed to constantly changing and new environment. It must gradually acquire the ability to adjust itself to differences in temperature and to new substances and materials of organic and inorganic structure, such as clothing of various fabrics, dust, various microorganisms, etc. The skin of some infants may be more sensitive than that of others and, therefore, more difficult of adjustment. Unless these adjustments are made gradually and intelligently, skin eruptions may ensue.

Soap is considered by many to be a frequent source of skin irritation in infants. Hansen[3] believes that soap, because of its alkalinity, very often causes skin irritation. Among adults, Jordan[4] and his co-workers found that 14 per cent of the normal persons gave a positive patch test reaction to diluted soap solution. The percentage rises to 50 among persons with some form of allergy. Goldman[5] tested newborn infants and children with soap solution and found that the newborn infants gave fewer positive reactions than did the older children.

Andrews[6] found that the scalp in children was the most neglected part of the skin area. Either it was not washed frequently enough, or, when washed frequently, was not supplied with sufficient oil after washing.

In our study we included, in the group of infants with folliculitis and dermatitis of the face, those who in the early weeks of life showed an erythematous, vesicular, papular, discrete eruption of the cheeks, forehead, and occasionally of the chin. Questioning invariably elicited the information that these infants were given frequent washings of soap and water as soon as they returned from the hospital. Rarely was this eruption found on any other part of the body. Occasionally a few vesicles or papules were noticed on the back and chest. Stopping the use of soap and water and application of a neutral powder brought complete cure in the majority of cases. If washing of the face was continued, the infant retained the facial eruption for some time, and it was later noticed that, in some cases, it assumed the clinical appearance of infantile eczema.

We also encountered a number of eruptions on the buttocks and the intertriginous areas of the thigh. Many studies of these eruptions have been made. Fox[7] calls these the intertriginous erythemas and feels that they are due to irritation caused by urine, feces, and decomposed sweat. He also distinguishes gluteal erythema of Jaquet which has a tendency to form papules, pustules, and superficial ulcerations. Montlaur[8] believes that erythema gluteale of Jaquet is due mainly to an internal enterococcus which he and his co-workers were able to isolate. The infant's skin becomes sensitized to this organism.

Our observations tend to suggest that both intertriginous erythema and gluteal erythema of Jaquet are different stages of the same eruption. In many of our cases, they coexisted, or the gluteal followed the intertriginous erythema. They start essentially as a chemical dermatitis, due to accumulated moisture from lack of evaporation, accompanied by maceration. Since some infants' skin is more sensitive to the decomposed chemicals of sweat, urine, and feces, irritation follows which finally results in pyogenic dermatoses. The finding of organisms is probably secondary. To counteract these intertriginous and gluteal eruptions, we recommend as early training of the toilet habit as is compatible with the child's development, frequent changes of the diaper which is to be rinsed in boric acid water after washing, application of liberal amounts of a neutral powder to the areas after rinsing off all soap solution, and the elimination of rubber panties.

The habit of overdressing infants in too many woolen, silk, and rayon clothes is, in our experience, a common cause of many skin eruptions. Despite many attempts to teach mothers not to use more than the necessary amount of clothing for children and to substitute loose clothing of cotton or linen, the tendency to overdress still persists. The

tender skin of the infant and child becomes irritated and macerated from decomposed sweat. Lack of evaporation of the sweat keeps the skin in a constantly moist state which serves as a good medium culture for various microorganisms. This fact has also been recognized by Marchionini and Ottenstein.[9] Riehl[10] states that continued attacks of dermatitis and miliaria due to tight and warm clothing may eventually result in a generalized protracted eczema.

The largest group of skin eruptions encountered in our study was the infantile eczema group. We observed all stages from the very mild one, characterized by erythema, papules, and scaling of the cheek, to generalized forms of the severest kind. Very often the same child progressed from the very mild to the severest stages or vice versa. This common skin ailment among children is so well known, and the literature is so full of contradictions and disappointments, that we thought it best to omit any review of the literature on this subject. However, we should like to present a few observations. Whenever possible, we attempted to correct any errors in the child's nutrition. Rarely did we find it necessary to withhold any basic food. We tried to limit the child's clothing and bedding to linen and cotton. We agree with Urbach[11] and Galewsky[12] that proper topical therapy is important in managing these infants' eruptions. Our experience has shown that topical applications for the treatment of infantile eczema are not skillfully applied, and that the first thought is usually to experiment with dietary regimes, occasionally with disastrous results to the child's development. In caring for these children, too great stress cannot be placed upon the need for proper nutritional and developmental care. In most cases, one should be able to manage the skin eruption by means of local applications.

SUMMARY

A study of the incidence of skin eruptions among 1,696 infants and preschool children is described.

Twenty-one per cent of this group showed skin eruptions during a nine-month period of observation.

Among the colored children in this group, the incidence of skin eruptions was only 16 per cent.

The incidence of skin eruptions was higher among infants than among preschool children.

The dermatidites and eczemas, including seborrheic eczemas, comprised most of the skin eruptions.

A great many of these eruptions are completely preventable, or, at least, their intensity and extent can be greatly reduced.

Suggestions have been presented for their management and care.

We wish to express our appreciation for their cooperation to Miss Mary Corke and Miss Alwina Gentsch, nurses-in-charge, respectively, of the Ridgewood and Jamaica Baby Health Stations.

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THE USE OF CONVALESCENT MUMPS SERUM

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AN OUTBREAK of epidemic mumps was thwarted by the use of 8 to 10 c.c. of convalescent serum given to fifty-one susceptible and exposed boys from 9 to 16 years of age while attending a summer camp. Of the fifty-one inoculated boys only one developed the disease, demonstrating a protective incidence of 98.04 per cent. When susceptible children are exposed to mumps, a resultant infection incidence of 30 to 50 per cent is to be expected. Without the use of serum in this study, between fifteen and twenty-five boys might have been expected to develop the disease.

Epidemics of any disease are dreaded by all camp directors, whether the camp be a military camp or a summer camp for children. Epidemic mumps are particularly dreaded because of the long incubation period and the unpleasant restrictions that are associated with the quarantine regulations. It is easy to conceive of an epidemic of mumps which might keep the camp under quarantine for the duration of the camping season or camp. Our larger summer camps draw children from distant parts of the country, and it is an annoying situation to have to inform parents, 300 and more miles away, that an epidemic of mumps has developed.

Such a problem was about to present itself in one of the largest boys' camps in the mountains of western North Carolina in July, 1939. Of the 125 boys attending this camp, 52 were known by their health records not to have had mumps. The first case of the disease developed in a 13-year-old boy while he was recovering in the camp infirmary from a sprained neck. The bilateral parotitis was not immediately recognized because of the restraining bandage applied by the orthopedic surgeon to the boy's neck and lower jaw. Twenty-four hours after the onset of fever the dressing was removed from the neck, and a typical bilateral parotid gland swelling was recognized and diagnosed as epidemic mumps by each of five medical consultants who happened to be visiting the camp at that time.

A search of the literature pertaining to the use of convalescent mumps serum as a prophylactic measure revealed very few references.

Hess,[1] in 1915, was the first to report the use of convalescent blood in the prophylaxis of mumps. The blood was supplied from (1) a group of children who had just recovered from the disease; (2) a group of children who had recovered ten days previously; and (3) another group who had recovered from one to two years previously. He recorded "no disagreeable manifestations or local reactions" from

doses of 6 to 8 c.c. of whole blood intramuscularly in seventeen children between the ages of 2 and 5½ years. In his series of seventeen susceptible and exposed children complete protection was obtained. In an untreated control group the infection incidence was between 33 and 50 per cent. He added that the blood of a parotitis patient possesses antibodies even before the glandular swelling has subsided and advised the use of blood from such patients when available. The duration of this type of immunity is unknown, but it certainly lasts beyond the period of incubation of the disease. Hess' work was begun in the midst of an epidemic, which he reported quickly terminated as a result of this type of prophylaxis.

Regan,[2] in 1925, studied the effects of giving 3 c.c. of convalescent serum to five groups of children, eighty-one in all, confined in a hospital. Convalescent serum was obtained from donors who had had the disease for from ten to twenty days. His patients received their injections from one to six days following exposure to the disease. The patients' ages were not recorded. On the basis of failure to protect in only one patient, he advised the use of 2 to 4 c.c. of convalescent serum from a recently ill patient before the seventh day following exposure.

Skrotsky,[3] in 1929, reported an epidemic of mumps in a hospital for contagious diseases in Odessa, in which 179 susceptible and exposed children were treated prophylactically with from 5 to 15 c.c. doses of convalescent serum. The two failures encountered were mild cases.

Barenberg and Ostroff,[4] in 1931, gave forty-four children 12 c.c. each of whole blood from a group of patients who had recovered ten days previously; to another group of eleven children he gave 12 c.c. each of whole blood from an adult who had had mumps as a child. He reported an infection incidence of 15 per cent in the treated group and an infection incidence of 39 per cent in the untreated control group. He believed his failures were due to the small amount of blood given each child. However, he observed that the duration of the epidemic was shortened. His reported findings, like those of Hess, point out the advantages of using blood from a recently recovered patient, as both of them used whole blood and not serum.

Zelig,[5] in 1932, used convalescent serum collected from six boys who had recovered from an attack of mumps within from six to thirty-two days. To each of forty-four boys, 10 to 18 years of age, he gave 5 c.c. of convalescent serum intramuscularly on the seventh day following exposure. Every boy was susceptible and had been definitely exposed to the disease. During the following three months not a single case of mumps developed.

Cambessedes[6] reported in 1933 on the use of mumps convalescent serum obtained from adults on the sixteenth to eighteenth day of the disease in a group of twenty-two orphanage girls, 6 to 16 years of age. He used 10 to 20 c.c. of the serum intramuscularly without a

failure to completely immunize. The author adds that orchitis in adults can be prevented by the use of 20 to 40 c.c. of serum before the fifth day of the disease.

Hinkley,[7] in 1937, reported the use of convalescent serum therapeutically with good results. He did not have a sufficient supply of serum available to use it prophylactically.

Thalhimer,[8] reporting before the eighth annual meeting of the American Academy of Pediatrics in June, 1938, stated that the prophylactic use of mumps convalescent serum "has been surprisingly good." In one series the intramuscular use of 20 c.c. protected forty-four out of forty-five children under 15 years of age. Another series showed 100 per cent protection in sixteen boys at a boys' camp. Two susceptible and exposed boys at this camp who did not take the serum developed the disease. Unfortunately, Thalhimer's report did not state specifically whether whole blood or separated serum had been used.

As previously stated, the first case to develop in this study occurred in a 13-year-old boy with an injured neck. Because of his popularity in the camp, as well as the nature of his injury, he was visited while in the infirmary by each of his fellow campers before it was discovered that, in addition to his injury, he also had mumps. By questioning it was learned that he had been visited by all of the susceptible boys on one or more occasions. The problem then was clear. Something had to be done at once which would protect the fifty-one boys who had not had the disease.

Convalescent blood was collected in a near-by hospital from one of the counsellors who had recovered from mumps one month previously, from the camp nurse who had had mumps three years previously, and from the camp physician, a patient ten years previously. From each donor approximately 500 c.c. of blood was taken, and a total of 550 c.c. of convalescent serum was recovered. Each portion of blood was handled separately until a report of a negative Wassermann reaction had been received, along with a negative forty-eight-hour plate culture. The sera were then pooled; another negative blood culture was reported before the serum was administered.

When the plan of procedure had been decided upon, the camp director, realizing the urgency of prompt action, advised each boy's parents of what was to be done to protect their boy against the disease. Many parents wrote or wired their acceptance of the plan, and not a single disapproval was received.

On the fourth day following the recognition of the first case of mumps in the camp the serum was ready. The fifty-one susceptible boys, from 9 to 16 years of age, were lined up, and to the younger and lighter weight boys 8 c.c. of convalescent serum were administered intramuscularly, and 10 c.c. were given to the older and heavier boys.

A history of allergy was known in ten boys; to each of these 0.1 c.c. of the serum was given intracutaneously. After forty-five minutes no serum reactions were observed at the site of testing. In none of the boys was there observed an immediate or delayed reaction to the serum.

The camp physician took each boy's temperature three times daily for the next three weeks. No febrile reactions followed the administration of the serum. Local reactions were absent except at the time of the following meal, when some of the boys scrambled to get the end seats on the benches in the dining room. All inoculations were given into the gluteal muscles. The only camp activity that was curtailed was swimming for the remainder of the day on which the inoculations were given. The remaining portion of the serum was administered to six adult counsellors and employees in 12 c.c. doses. All of them likewise escaped the disease.

The only failure to completely protect against the disease occurred in a 13-year-old boy ten days after he had received the serum and fourteen days following exposure. He developed bilateral mumps and ran a course typical of a mild form of the disease. The first case developed thirteen days after the opening of the camp; the second, ten days later.

The camp was operated during the months of July and August, all boys being present for the entire eight weeks. With an incubation period of twenty-one days, there was ample time for the immunized boys to develop the disease between July 13, when the first case was recognized (or July 23, when the second case developed), and August 28, when the camp closed. Since it is known that the incubation period of measles is sometimes prolonged when immune measles globulin is used prophylactically, it was suspected that the convalescent serum might similarly prolong the incubation period for mumps. However, after five weeks no additional cases had developed, and none developed before the close of camp.

SUMMARY

With a reported incidence of 30 to 50 per cent in exposed and susceptible children following exposure to mumps, an infection incidence of the disease in between fifteen and twenty-five boys might have been expected. The much lower infection incidence of only 2 per cent was attributed to the use of 8 to 10 c.c. of convalescent mumps serum in fifty-one boys, between the ages of 9 and 16 years, on the fourth day following exposure.

CONCLUSIONS

Mumps, while not a dangerous disease in childhood, is a disease dreaded by all directors of summer camps because of its contagious nature and the long-drawn-out quarantine it necessitates.

The available literature on the use of mumps convalescent serum is reviewed.

The procedure of collecting and administering convalescent mumps serum is outlined in detail.

In this study satisfactory results were obtained in the complete immunization of fifty-one boy campers against mumps by the use of small doses of convalescent serum on the fourth day following exposure to the disease.

To Mr. Walton Johnson, director, and Arthur C. Darrow, M.D., of Camp Sequoyah, I wish to express my grateful appreciation for their cooperation in making this study possible.

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THE VOLLMER TUBERCULIN PATCH TEST

Evaluation of Its Relative Sensitivity

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SINCE the introduction of the Vollmer (Lederle) tuberculin patch test in 1937,[1] subsequent investigations[2-6, 8] have served to corroborate the original observations and to establish further the value of this test in the detection of tuberculin-sensitive individuals. The Vollmer (Lederle) tuberculin patch test (hereinafter called the patch test) has been critically compared with the von Pirquet and Mantoux tuberculin skin tests in attempts to establish the relative value of the patch test. It is the purpose of this paper to correlate the relative sensitivity of the patch test with the Mantoux intradermal test performed with solutions of purified protein derivative, and to review briefly some of the features of the patch test.

METHOD

The technique of application of the patch test is that recommended by Vollmer and Goldberger.[3] The tuberculin patch test consists of a piece of adhesive tape 2.5 by 7.5 cm., on which are placed near the ends two 1 by 1 cm. squares of filter paper saturated with undiluted tuberculin produced from a synthetic medium (after Seibert[7]), and in the middle of which is a control square of filter paper saturated with glycerin broth. The dried tuberculin present in the filter paper squares is liquefied by insensible perspiration after application to the skin, and the resultant solution produces the positive tuberculin reaction.

An area of skin (in our cases either over the sternum or in the interscapular area) is cleansed with acetone, ether, or purified petroleum benzine. The protective crinoline layer is then removed from the adhesive tape, exposing the patch tests and the control square. The adhesive tape is then applied firmly over the cleansed area, and the patient is instructed not to allow the tape to become wet. After forty-eight hours the patch test is removed, and forty-eight hours later the reading of the test is performed.

A positive reaction consists of a reddened, indurated area with lichenoid follicular elevations, as is shown in Figs. 1, 2, and 3. Usually the reaction has a clear-cut square shape, corresponding to the area covered by the filter paper saturated in tuberculin, but occasionally the reaction spreads beyond the zone of the patch and covers an irregular area. More rarely a blister forms at the site of the patch test (Fig. 4). Reactions from the control square offer practically no difficulty in differentiation.

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No general reactions are noted, but transitory local itching and burning are frequently present in persons with positive tests. Pigmentation persists for several days or two weeks.

Vollmer and Goldberger[1] have expressed in the following manner the advantages of the patch test over other tuberculin tests:

"1. It is painless and does not excite nervous children, and a good relation between the doctor and the patient is thus retained.

"2. It consumes less time.

"3. It does not involve the use of instruments and their sterilization, or trauma to the skin through injection, scarification, or rubbing.

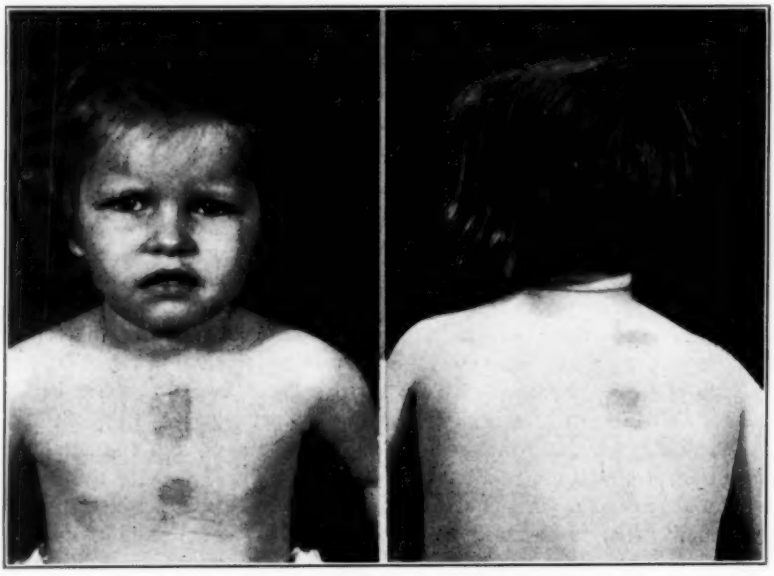

Fig. 1. Fig. 2.

Fig. 1.—Typical positive tuberculin patch test reaction. In this instance the reaction consisted mainly of an erythematous area, with only a slight degree of lichenoid follicular elevation.

Fig. 2.—Same patient showing a positive tuberculin patch test reaction in the right interscapular area. The patch test is as sensitive when applied in the interscapular area as it is when applied over the sternum.

"4. It can be carried out without help, or by a nurse or an assistant.

"5. In contrast to all other patch tests, it creates a sharply limited area of reaction and prevents an uncontrollable spread of tuberculin on the skin.

"6. It eliminates the danger of infection.

"7. It has never led to local or general constitutional reaction."

HISTORICAL DATA

Vollmer and Goldberger[1] have reviewed the subject of tuberculin patch tests from a historical standpoint, describing the difficulties encountered in previous attempts to perfect a reliable and useful tuberculin patch

test. In their report the Vollmer (Lederle) tuberculin patch test was compared with the von Pirquet test with the following results:

Of 209 children tested, most of whom had active tuberculosis, 89.5 per cent showed a conformity between the results of the patch test and the von Pirquet test. Of the 209, 7.2 per cent showed a negative reaction to the von Pirquet test and a positive reaction to the patch test; 3.3 per cent had a negative reaction to the patch test and a positive reaction to the von Pirquet test. These figures indicate that the patch test is a more sensitive test than that of von Pirquet.

Fig. 3. Fig. 4.

Fig. 3.—Positive tuberculin patch test reaction illustrating erythematous, lichenoid, follicular elevations. This was the most common type of reaction noted.

Fig. 4.—Positive tuberculin patch test reaction in the right interscapular area illustrating the formation of superficial blebs. This was the most severe type of reaction noted.

In a later paper Vollmer and Goldberger[2] compared the patch test with the Mantoux intradermal test with the following results:

Of 169 children with active tuberculosis, only one who reacted positively to the Mantoux test with the stronger solution of purified protein derivative failed to react positively to the tuberculin patch test.

Among 118 children admitted with various diseases and tested routinely, the Mantoux test, even when 1 mg. of old tuberculin was used, did not reveal a single case of tuberculous infection which had not already been discovered by the patch test.

Steward[4] found 98 per cent correlation between the patch test and the 1:1,000 Mantoux test in ninety-one tuberculous children in a sanatorium

and in five normal adults. All six patients who did not have similar results from the tests had positive patch tests and negative 1:1,000 Mantoux tests. Steward's results indicate a definite superiority of the patch test over the 1:1,000 Mantoux test.

Hart[5] tested routinely 536 children with the Mantoux test in varying dilutions, with the Vollmer (Lederle) patch test, and with the Copenhagen patch test with *Tuberkulinsalve*. Only the results of the Vollmer (Lederle) patch tests and the Mantoux tests will be analyzed here. Only 100 of the 536 children had positive Mantoux tests. All 436 children with negative Mantoux tests also had negative patch tests. Of the 100 Mantoux-positive cases, 96 had positive patch tests. In the four cases in which the patch test was negative and the Mantoux test was positive, the Mantoux test had to be employed in 1:100 strength in order to get a positive result. All the cases who reacted positively to the 1:10,000 or 1:1,000 Mantoux tests also had positive patch tests.

Hart's results indicate that the patch test is as sensitive as the 1:10,000 or the 1:1,000 Mantoux intradermal test, but is less sensitive than the 1:100 Mantoux test. It will be noted that these results are contrary to Steward's findings which showed a definite superiority of the patch test over the 1:1,000 Mantoux test. They are also contrary to the report of Vollmer and Goldberger[2] that, among 118 children routinely tested, the Mantoux test, even when 1 mg. of old tuberculin was used, did not reveal a single case of tuberculous infection which had not already been discovered by the patch test.

Hart suggests that the stronger dilutions of the Mantoux test may give too many positive reactions (false positive reactions) and that the patch test may give too few positive reactions (false negative reactions). However, these suggestions are not supported by any data.

In their third paper concerning the patch test Vollmer and Goldberger[3] reported the following results:

Among 417 children routinely tested with 0.1 mg. of old tuberculin and tested simultaneously with the patch test the reliability of the patch test as compared with the Mantoux test was 100 per cent. Two hundred and sixty-one tuberculous children showed 100 per cent conformity between the patch test and the Mantoux test with first strength solution of purified protein derivative or with 0.01 to 1 mg. of old tuberculin. One child who was negative to the patch test reacted positively to the Mantoux test with second strength solution of purified protein derivative. The authors concluded that the Mantoux test with 0.1 mg. of old tuberculin or less, or with first strength solution of purified protein derivative, can be safely replaced by the tuberculin patch test.

Weiner and Neustadt[8] applied the patch and von Pirquet tests routinely to 257 children. In 200 cases both tests were negative. In forty-four cases both tests were positive. In thirteen cases there was disagreement between the patch test and the von Pirquet test, ten of the cases having positive patch tests and negative von Pirquet tests, while

three had positive von Pirquet tests and negative patch tests. The authors concluded that the patch test was about as satisfactory as the von Pirquet test in routine tuberculin testing. However, their figures show a slight superiority of the patch test over the test of von Pirquet. Of sixty-three patients who were negative to patch and von Pirquet tests, three were found positive to a 1:1,000 Mantoux test, leading the authors to conclude that the patch test is about 95 per cent as effective as the Mantoux 1:1,000 intradermal test. Because of negative chest roentgenograms in two children who reacted positively to the patch test and negatively to the 1:1,000 Mantoux test, the authors assume that the patch tests in these two instances were falsely positive. However, proof of this conclusion is lacking because it is well known that tuberculin-sensitive persons may react negatively to the 1:1,000 Mantoux intradermal test and that they may also, and frequently do, have negative chest roentgenograms.

Peck and Wegman[9] tested 880 children routinely with the patch test and with first and second strength solutions of purified protein derivative in a manner almost identical to that used in the series to be reported in this paper. The patch test was found to be positive in only 30 per cent of the tuberculin-positive patients; the test with first strength solution of purified protein derivative was positive in 41 per cent of the tuberculin-sensitive children, while the test with second strength solution of purified protein derivative was positive in 100 per cent of the tuberculin-sensitive cases. This report by Peck and Wegman is the most discouraging record in the literature concerning the patch test, and one wonders why the degree of sensitivity to the patch test was so low in their series. In addition, one wonders why so few of the patients, 41 per cent of the positive cases, reacted positively to the test with first strength solution of purified protein derivative.

Vollmer and Goldberger[10] have recently shown that the tuberculin patch test is more sensitive when the filter paper squares have been soaked in old tuberculin than when saturated with purified protein derivative solution. They ascribe this increased sensitivity to the greater water content of old tuberculin which facilitates a more rapid reaction.

PERSONAL EXPERIENCE WITH THE PATCH TEST

In the Department of Pediatrics of the John Gaston Hospital, and in the Pediatric Outpatient Department of the University of Tennessee, related departments, an attempt has been made to correlate the sensitivity of the patch test with the Mantoux intradermal test performed with solutions of purified protein derivative (hereinafter called P.P.D.). All children admitted to the hospital or to the outpatient department were routinely tested with the first strength P.P.D. All negative reactors were then tested with the second strength solution of P.P.D. All patients reacting positively to either of these two intradermal tests were immediately examined by means of the patch test.

Obviously, such a plan of procedure tended to favor the intradermal test at the expense of the patch test, since no patients who were negative to the intradermal test were tested with the patch test. This procedure ruled out any possibility of finding cases in which the patch test was positive when the intradermal test was negative, but it did allow cases to be found in which the patch test was negative and the intracutaneous test positive. In spite of the handicap inherent in such a plan it will be seen that the patch test compared very favorably with the intradermal tests using solutions of P.P.D.

One hundred cases in which the intradermal tests with P.P.D. solutions were positive were tested by means of the patch test. Seventy-eight of these cases reacted positively to the first strength solution of P.P.D., while twenty-two reacted positively only to the second strength solution of P.P.D.

Of the 100 cases, 89 reacted positively to the patch test and 11 reacted negatively.

Of the seventy-eight cases with positive reactions to the first strength solution of P.P.D., all had positive patch tests.

There were eleven cases in which the patch test was positive but in which the test with first strength solution of P.P.D. was negative, showing a very definite superiority of the patch test over the first strength solution of P.P.D. in this series of patients.

There were eleven cases in which the patch test was negative but in which the test with second strength solution of P.P.D. was positive, showing that the patch test is inferior to the second strength P.P.D. test.

Expressed differently, 78 per cent of all the tuberculin-sensitive patients would have been detected by testing with the first strength solution of P.P.D. alone; 89 per cent would have been detected by the patch test alone; and the remaining 11 per cent would have been detected by the second strength solution of P.P.D.

From these results the conclusions can be drawn that the tuberculin patch test is definitely superior to the Mantoux intradermal test with first strength solution of P.P.D., but that it is inferior to the Mantoux test with second strength solution of P.P.D. We agree with Vollmer and Goldberger that the test with first strength solution of P.P.D. can be safely replaced with the tuberculin patch test.

The age of the patient had no bearing on the correlation of patch and intradermal tests in this series of patients. This is contrary to the statement of Logie[6] who says: "My experience with the Vollmer (Lederle) test in large-scale testing of children justifies the use of the test as a reliable method in children below 5 or 6 years of age. In this group a negative patch test may be accepted, without retest, as a reliable indication of the absence of any significant tuberculous lesion."

In studying the patch test it was decided to examine a series of patients in whom the patch test was applied simultaneously on the skin over the sternum and on the skin of the right interscapular area. The

purpose of this study was to determine whether the test on the back, which has the obvious advantages in that it cannot be easily removed by the child and that it can be applied with less fright to the patient, is as reliable as the test on the anterior surface of the chest. Theoretically, of course, there would seem to be no reason to suppose a local difference in skin tuberculin-sensitivity existed. The following results were obtained:

The patch test was applied on the front and back of the chest simultaneously in 70 cases. Nine cases showed negative reactions at both sites. Fifty-eight cases showed positive reactions on the front of the chest, while sixty cases had positive reactions on the back. There was one case in which the patch test was positive on the front and negative on the back, but there were two cases in which the patch was positive on the back and negative on the front. The results in this small series of patients would indicate that the tuberculin patch test is as reliable when placed in the interscapular area as it is when placed over the sternum. The practical implications of this observation are that the child is less frightened by the application of the patch on the back, and that the patient is unable to pull the patch off, either from juvenile curiosity or from irritation of the skin incident to a markedly positive reaction. Several of the patch tests which were applied over the sternum were pulled off by the children, and in almost every case a markedly positive reaction had occurred. Cases in which the patch had been pulled off and in which the test was not positive are not included in the statistics previously given relative to comparative efficiency of back and front patch tests.

In our series of cases there were no general reactions from positive patch tests, even when two tests were applied simultaneously. The most commonly observed reactions were local itching and burning sensations which subsided rather rapidly after the patch was removed. After removal of the patch in a strongly positive test, calamine lotion was occasionally prescribed to control the mildly unpleasant itching and burning. There were no instances of necrosis of the skin, although in a few cases large blebs occurred which were very superficial and comparable to only a slight extent with the necrosis seen at times in markedly positive intradermal tests. We have encountered cases in which the intradermal test with first strength solution of P.P.D. gave a doubtfully positive reaction, but in which the subsequent application of the test with second strength solution of P.P.D. resulted in necrosis of the skin, with lymphangitis and adenitis at times. In none of the cases in which the patch test was negative but the test with second strength solution of P.P.D. positive was the intradermal test more than mildly positive. The great difference in strength of the first and second strength solutions of P.P.D. may thus lead to necrosis when the second strength solution is employed after a doubtfully positive first strength test, but the difference in sensitivity between the patch test and the

second strength P.P.D. test is so slight that such necrosis is not likely to occur. In our opinion, this is one of the definite advantages of replacing the intradermal test with first strength solution by the patch test.

Many of the patients were negroes in whom depigmentation from the patch test would be detected readily if it occurred; no such depigmentation was noted. The pigmentation incident to positive reactions went away without fail within two weeks after removal of the patch. The control square of filter paper saturated in glycerin broth produced no reactions on the skin in any of our cases.

SUMMARY

1. A historical review of the evaluation of the Vollmer (Lederle) tuberculin patch test is given.

2. The method of applying the test is discussed briefly.

3. A study of one hundred tuberculin-sensitive cases is presented, correlating the patch test with the intradermal tuberculin tests with solutions of purified protein derivative.

4. The patch test is shown to be more sensitive than the intradermal test with first strength solution of purified protein derivative and less sensitive than the intradermal test with second strength solution of purified protein derivative.

5. In this small series of patients the efficiency of the test with first strength solution of purified protein derivative is rated at 78 per cent, the efficiency of the patch test at 89 per cent, and that of the test with solution of second strength purified protein derivative at 100 per cent.

6. The results obtained give further basis to the belief that the patch test may be used in preference to the intradermal test with first strength solution of P.P.D.

7. The patch test, in our experience, is definitely inferior to the intradermal test with second strength solution of P.P.D.

8. The tuberculin patch test is as sensitive when applied in the interscapular area as it is when applied over the sternum, and there is less chance of the child's removing the patch.

9. No significant reactions, other than local phenomena, were noted when the patch test was used.

The Vollmer (Lederle) tuberculin patch tests used in this study were furnished by The Lederle Laboratories, Inc.

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2 NORTH SOMERVILLE STREET

EFFECTS UPON MONKEYS OF SULFAPYRIDINE IN DOSES COMPARABLE WITH THOSE USED FOR INFANTS

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I.

IN A previous experiment, twelve *Macacus malatta* monkeys were each given sulfapyridine through a catheter passed into the stomach, the dosage being 0.5 gm. of the drug in 10 c.c. of water twice a day for ten days, 10 gm. in all. Two other animals received varying amounts of the drug for fifty-two days, each one having been given approximately 27 and 32 gm., respectively. Thirteen of the fourteen animals died and were subjected to complete autopsy. Grossly, the findings in the urinary tract were similar and characteristic in all thirteen animals.[1]

The blood sulfapyridine level taken at irregular intervals in eight animals ranged from 1.2 mg./100 c.c. to 8.2 mg./100 c.c. Specimens for blood urea nitrogen (B.U.N.) determinations were taken simultaneously in these animals. They ranged from 33.8 mg./100 c.c. to as high as 160.4 mg./100 c.c. There was a decrease in the total number of red blood cells and in their hemoglobin content. Since most of these monkeys were ill with poliomyelitis,[2] the effects caused solely by the drug could not be accurately determined.

The recommended dose of this drug for patients ill with pneumonia depends upon physical signs.[3] Adults are given 4 gm. immediately, followed by 1 gm. every four hours until the temperature becomes normal and has remained thus for at least forty-eight hours. In approximating the dosages, it was assumed that the temperature would come down within the first twenty-four hours. Subsequently, the dose is decreased to 1 gm. every six hours until the pneumonic process begins to resolve. The time when this happens is indefinite, but usually it is approximately from the fourth to the sixth day of the infection. The drug is then continued, giving 0.5 gm. four times a day until the lungs are clear. By physical signs this usually does not occur before the fifteenth day, and if x-ray evidence is considered, not even by that time. The total initial and subsequent doses for children are less and depend upon the weight of the child. The doses estimated in Table I were based upon the considerations noted above.

From the Department of Pediatrics and Institute of Pathology, Western Reserve University, and the Departments of Contagious Diseases and Pathology, City Hospital. Aided by a grant from The Cleveland Foundation.

TABLE I

DAY	ADULTS	TOTAL GRAMS	CHILDREN	TOTAL GRAMS	INFANTS	TOTAL GRAMS
1st	4 gm. immediately; 1 gm. q. 4 h.	10	2 gm. immediately; 1 gm. q. 4 h.	8	1 gm. immediately; 0.5 gm. q. 4 h.	4
2nd and 3rd	Temperature normal first day; 1 gm. q. 4 h.	12	1 gm. q. 6 h.	8	0.5 gm. q. 6 h.	4
4th to 6th*	Resolution probably under way; 1 gm. q. 6 h.	12	0.5 gm. q. 6 h.	6	0.25 gm. q. 6 h.	3
7th to 15th*	Lungs clear 15th day by physical signs, but not by x-ray; 0.5 gm. Q.I.D.	18	0.25 gm. q. 6 h.	9	0.125 gm. q. 6 h.	4.5
	Total	52		31		15.5

*Inclusive.

II.

A second set of experiments was planned to determine the effect of sulfapyridine on normal *M. malatta* monkeys weighing approximately 3 kg. In a preliminary experiment the B.U.N. levels of eight normal animals were determined, the average being 13.9 mg./100 c.c. as noted in Table II. The same animals had negative blood sulfapyridine levels. The doses of the drug to be given were those recommended for infants of comparable weights. Theoretically, infants weighing 3 kg. might get 15.5 gm. of the drug. It was found that this amount was excessive and invariably produced typical lesions of the urinary tract in monkeys, so the total dose in the experiments immediately following was decreased to 10 gm. for an animal weighing 3 kg. This was a dose less than that usually recommended for infants and younger children, but comparatively greater than that recommended for older children and adults. *In the following experiments, save where otherwise noted, the drugs were introduced into the stomach through a small catheter.*

The method and material employed and the findings in all the experiments are recorded in Tables II and III.

EXPERIMENT I.—Animal No. 1997, the starting control, received 0.5 gm. of sulfapyridine in 10 c.c. of saline twice a day for ten days. There was a drop in the total number of red blood cells and their hemoglobin content, an increase in the total number of white blood cells, and a rise in the B.U.N. level.

At autopsy the positive findings were as follows: emaciation, ascites, abdominal parasitosis, bilateral hydroureters, and hydronephrosis. The pelvis of the kidney contained urine and many crystals. The urinary bladder held less than 1 c.c. of urine. Microscopic examination showed that the lumina of both ureters were blocked by crystals. There were severe hyperemia and an infiltration of lymphocytes in all coats of the ureters, the infiltration being particularly severe in the adventitia. There were perivascular collections of round cells of the myeloid type in the cortex and medulla of the kidneys. The ostia of the straight tubules pouted into the kidney pelvis at the tip of the papillae, and one tubule contained crystals. There

was considerable granularity of the cytoplasm of the cells lining the convoluted tubules. The submucosa of the pelvis of the kidney was infiltrated with lymphocytes. There was a severe degree of hyperemia and a small number of lymphocytes in the submucosa of the bladder. (Fig. 1.)

When the pathologic lesions, as described in Experiment I, were present in the urinary tract of an experimental animal, such an experiment was termed "positive" in the tables.

EXPERIMENT II.—An attempt was made to render the urine alkaline to see if it would have any effect on the formation of crystals (Table II).

The two monkeys given sulfapyridine combined with potassium citrate were more severely ill clinically than was control animal No. 1997. Both animals became ill within twenty-four hours after the experiment was started, one dying the third and the other the sixth day following the initial dose. One had ingested 3 gm., and the other, only 6 gm. of the drug.

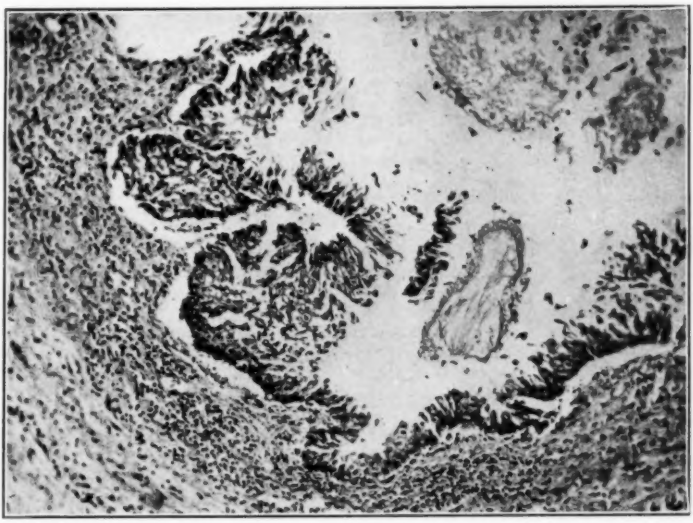

Fig. 1.—Monkey No. 1997. Photomicrograph showing crystals in pelvis with lymphatic infiltration of the submucosa. (Hematoxylin-eosin, ×129.)

Both animals had positive findings. In addition, animal No. 2103 (which received 3 gm. of the drug) had a calculus in the bladder measuring 2 mm. The epithelium of the pelvis of the kidney showed early metaplasia, focal necrosis, and hemorrhages. The urethra showed degenerative changes of the mucosa, with an infiltration of polymorphonuclear cells in the submucosa.

In animal No. 1999, the collecting tubules in the papillae contained crystals, and there was an area of infiltration with polymorphonuclear cells. The submucosa of the pelvis was also infiltrated with these cells.

EXPERIMENT III.—An attempt was made to render the urine acid to see if this would have any effect on the formation of crystals (Table II).

Animals No. 2100 and No. 2104 were killed when the mixture of ammonium chloride and sulfapyridine was accidentally introduced into the lungs. It should be noted that the B.U.N. of No. 2104, taken the day of death, was 39.4 mg./100 c.c.,

TABLE II

EXP. NO.	ANIMAL NO.	DRUG, DOSAGE, AND METHOD OF ADMINISTRATION	HEMOGLOBIN %	RED BLOOD CELLS	WHITE BLOOD CELLS	DIFFERENTIAL		pH		CRYSTALS (DAY)	R.B.C. (DAY)	MG. %		PATHOLOGIC LESIONS
						POLYMORPHONUCLEARS (%)	LYMPHOCYTES (%)	BLOOD	URINE			BLOOD SULF. LEVEL	B.U.N. LEVEL*	
												(Day)		
I	1997	Sulf. 0.5 gm. B.I.D. by mouth in 10 c.c. saline for 10 days.	(a)† 80	5.40	9,800	65	29	7.5	6.8	6th	6th	1st: 0	13.9*	
			(b)‡ 45	2.93	16,100	86	9	7.5	7.4			4th: 3.6	50.5	+
												10th: 7.6	46.3	
II	1999	Sulf. 0.5 gm. and K citrate 0.5 gm. combined in 10 c.c. saline. B.I.D. by mouth. Lived 6 days.	(a) 80	5.56	18,700	62	31	7.5	6.8	2nd	2nd	1st: 0	13.9*	
			(b) 75	5.75	27,500	87	11	7.5	7.8			4th: 5.6	54.5	+
												5th: 3.0	93.6	
	2103	Same as No. 1999. Lived 3 days.	(a) 80	5.62	18,000	68	28	7.5	6.8	2nd	2nd	1st: 0	13.9*	
			(b) 65	3.80	21,700	69	28	7.5	7.5			3rd: 6.0	46.9	+
III	2100	Sulf. 0.5 gm. and NH_4Cl 0.5 gm. each in 10 c.c. saline. B.I.D. by mouth for 10 days. Lived 36 hours.	(a) 80	5.99	17,300	69	27	7.5	6.8			1st: 0	13.9*	
												No blood chemistry		-
			Animal died on 2nd day due to accidental introduction of drug into lungs.											
	2104	Same as No. 2100. Lived 24 hours.	(a) 80	6.13	12,500	72	25	7.5	6.8			1st: 0	13.9*	
			Also died on 2nd day due to same cause as in No. 2100.									2nd: 0	39.4	-

*13.9 = Average B.U.N. level.
†(a) = start of experiment (first day).
‡(b) = end of experiment (last day).

TABLE II—CONT'D

	2101	Same as No. 2100.	(a)	80	4.75	24,500	49	40	7.5	6.8	3rd	5th	1st: 0	13.9*	
			(b)	45	2.65	18,350	61	34	7.5	5.8			5th: 2.0	27.7	-
													8th: 1.6	19.5	
	2105	Same as No. 2100.	(a)	80	5.80	16,000	55	40	7.5	6.8	7th	7th	1st: 0	13.9*	
			(b)	60	3.95	15,600	53	42	7.5	5.6			10th: 1.0	9.1	-
	2115	Same as No. 2100. Lived 8 days.	(a)	80	5.30	26,800	53	38	7.5	6.8	5th	5th	1st: 0	12.6	
			(b)	55	3.92	19,500	91	8	7.5	5.8			7th: 3.8	89.2	+
IV	1998	Sod. Sulf. 0.5 gm. in 10 c.c. saline B.I.D. by mouth. Lived 4 days.	(a)	80	5.84	18,850	69	27	7.5	6.8	2nd	2nd	1st: 0	13.9*	
			(b)	65	4.26	32,500	87	9	7.5	7.6			4th: 33.6	81.2	+
	2102	Same as No. 1998. Sacrificed on 10th day.	(a)	80	5.87	27,200	81	16	7.5	6.8	2nd	2nd	1st: 0	9.8	
			(b)	55	4.00	8,000	53	42	7.5	7.3			10th: 11.4	58.5	+
V	2116	Sod. Sulf. 1.0 gm. in 10 c.c. saline by vein daily and 0.5 gm. NH_4Cl in 10 c.c. saline by mouth B.I.D. Died 2nd day.	(a)	75	5.00	27,200	66	32	7.5	7.0	2nd	2nd	1st: 0	12.3	
			(b)	70	4.33	18,400	82	15	7.5	7.6			2nd: 60.0	75.5	+
	2117	Same as No. 2116. Lived 2 days.	(a)	80	5.80	21,500	48	48	7.5	6.8	1st	1st	1st: 0	15.4	
			(b)	75	5.40	20,800	50	46	7.5	7.8			2nd: 29.6	50.0	+
VI	2118	Sulf. 0.5 gm. in 10 c.c. saline by mouth B.I.D. for 10 days. Daily infusion of 100 c.c. of saline subcutaneously.	(a)	80	5.20	22,900	62	36	7.5	6.8	6th	6th	1st: 0	14.0	
			(b)	60	3.64	11,000	60	34	7.5	7.0			10th: 4.1	55.0	+
	2119	Same as No. 2118.	(a)	80	5.70	22,000	89	10	7.5	6.8	6th	10th	1st: 0	18.2	
			(b)	60	3.39	18,750	64	39	7.5	6.5			10th: 1.5	27.3	+
VII	2106	5 c.c. 10% sulfapyridine in 50% glucose given I.V. B.I.D. for 10 days.	(a)	80	5.40	8,750	48	47	7.5	6.8	None	None	1st: 0	15.9	
			(b)	55	3.53	17,100	16	80	7.5	6.8			10th: 0.3	25.8	-
	1986	10 c.c. 10% sulfapyridine in 50% glucose given intravenously daily for 10 days.	*Day*												
			1st:	70	4.72	16,000	62	35	7.5	6.8	9th	None	1st: 0	10.2	
			6th:	60	3.53	6,950	40	55					12th: 0	16.1	
			12th:	70	4.54	8,250	36	57	7.5	7.6					-

TABLE III

EXP. NO.	ANIMAL NO.	DRUG, DOSAGE, AND METHOD OF ADMINISTRATION		HEMOGLOBIN %	RED BLOOD CELLS	WHITE BLOOD CELLS	DIFFERENTIAL POLYMORPHONUCLEARS (%)	DIFFERENTIAL LYMPHOCYTES (%)	pH BLOOD	pH URINE	CRYSTALS (DAY)	R.B.C. (DAY)	MG. % BLOOD SULF. LEVEL (Day)	MG. % B.U.N. LEVEL‡	PATHOLOGIC LESIONS
VIII	2108	Sulfapyridine by mouth once a day for 15 days in graduated doses. Noted in text.	(a)*	80	6.12	12,700	53	40	7.5	7.5	3rd	9th	1st: 0	14.7	-
			(9th)				76	20							
			(11th)				28	63							
			(b)† (15th)	70	4.38	11,900	16	80	7.5	6.0			15th: 0	15.1	-
	2109	Sulfapyridine by mouth as No. 2108 and NH_4Cl 2 gm. in 10 c.c. saline daily by mouth. Lived 2 days.		80	6.10	21,950	38	66	7.5	7.3					-
	2122	Sulfapyridine by mouth as No. 2108 and NH_4Cl 0.5 gm. in 10 c.c. saline once a day for 15 days.	(a)	75	4.65	38,000	83	14	7.5	6.8	None	None	1st: 0		
			(b)	75	4.89	34,380	67	30	7.5	7.4			15th: 0.5	9.1	-
	2110	Sulfapyridine by mouth as No. 2108 and K citrate 2 gm. in 10 c.c. saline by mouth for 15 days.	(a)	75	4.48	14,450	45	49	7.5	7.0	None	None	1st: 0	10.9	
			(b)	75	4.58	12,900	38	60	7.5	--			15th: 0	7.0	-
	2112	Sodium sulfapyridine by mouth once a day (same dosage in No. 2108). Animal died 12 days later.	(a)	80	4.40	14,650	30	64	7.5	7.2	5th	5th	1st: 0	6.3	
			(b)	60	2.92	28,250	74	22	7.5	7.6			12th: 7.6	81.6	+
	2111	10% sulfapyridine in 50% dextrose solution once a day by mouth for 15 days.	(a)	80	4.71	27,150	50	46	7.5	6.6	5th	5th	1st: 0	11.9	
			(b)	80	5.20	22,200	59	37	7.5	7.8			15th: 0.5	10.2	-
	2121	Same dosage as No. 2111, by vein for 15 days.	(a)	70	4.10	11,800	65	32	7.5	6.8	8th	8th	1st: 0	14.7	
			(b)	70	4.08	11,400	34	63	7.5	5.6			15th: 0.4	24.2	-

*(a) = start of experiment (first day).
†(b) = end of experiment (last day).
‡13.9 = Average B. U. N. level.

and this after only 1 gm. of the drug had been given. However, the effects of ammonium chloride were not determined.

At autopsy, animal No. 2115 had positive findings in addition to hemorrhages under the capsule of the liver and in the lungs. The submucosa of the renal pelvis and the papillae were the seats of hemorrhage and severe suppurative inflammation. There were thrombi in vascular spaces (probably veins) of the pyramids, perivascular cuffing with lymphocytes, and focal areas of lymphocytic infiltration in the cortex (Fig. 2).

Animals No. 2101 and No. 2105 had negative findings at autopsy, although in the latter animal there was a slight granularity of the tubular epithelium of the kidney.

EXPERIMENT IV.—Sodium sulfapyridine was used instead of sulfapyridine in this experiment. Animals No. 1998 and No. 2102 became ill within twenty-four hours after ingestion of the drug. The former died four days later, having received 4 gm. of the drug; the latter lived to be sacrificed ten days after the experiment had been started.

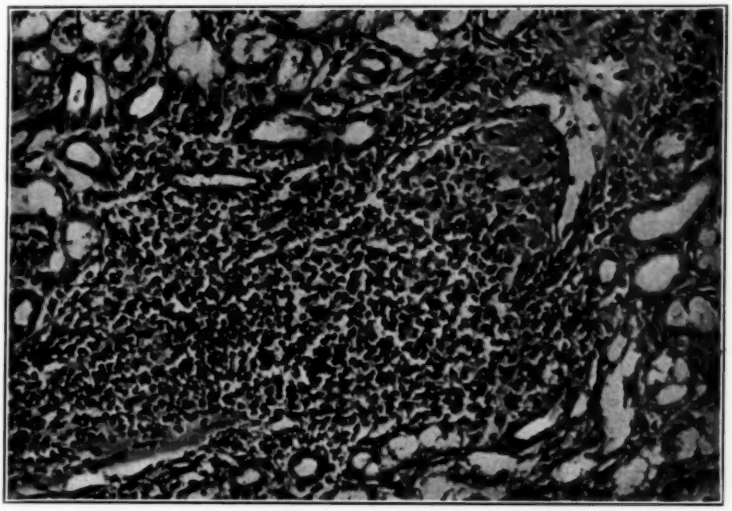

Fig. 2.—Monkey No. 2115. Photomicrograph showing thrombosis of vascular spaces in kidney with acute suppurative inflammatory reaction. (Hematoxylin-eosin, ×276.)

Both these animals had positive findings. In No. 1998, the number of crystals in the kidneys was great enough to encrust the tips of the pyramids. White streaks appeared along the straight tubules. Microscopically, crystals were found imbedded in pus within the tubules (Fig. 3). In animal No. 2102, there were hemorrhages in the rectovesical fossae and in the pelvis of the left kidney. The degree of crystal formation was as great as that seen in animal No. 1998.

EXPERIMENT V.—Sodium sulfapyridine was given by vein and ammonium chloride by mouth. Both animals, No. 2116 and No. 2117, became ill and had anorexia immediately after the experiment started; both died two days later. They did not live long enough for clinical signs to develop, although red blood cells and crystals were found in the bladder urine collected at post mortem. The additional toxic effect of ammonium chloride could not be evaluated, so that this experiment was inconclusive.

B.U.N. and blood sulfapyridine levels on the day of death were 75.5 mg./100 c.c. and 60.0 mg./100 c.c., respectively, figures which are not valid, since the blood was withdrawn shortly after the injection of sulfapyridine.

Animals No. 2116 and No. 2117 had severe positive findings. In the former, the pelvis of the right kidney was filled with a mass of crystalline material.

EXPERIMENT VI.—It is difficult to have monkeys take proper amounts of fluid. It is conceivable that crystals are formed because the urine is too concentrated. Hence, monkeys No. 2118 and No. 2119 were each given 0.5 gm. of sulfapyridine in 10 c.c. of saline twice daily for ten days and also a daily subcutaneous infusion of 100 c.c. of saline. Absorption was slow, and dependent edema developed after the fourth day.

Clinically, there was a decrease in the number of red cells and in hemoglobin content. One of the animals had an increase of the circulating lymphocytes from 10 to 39 per cent.

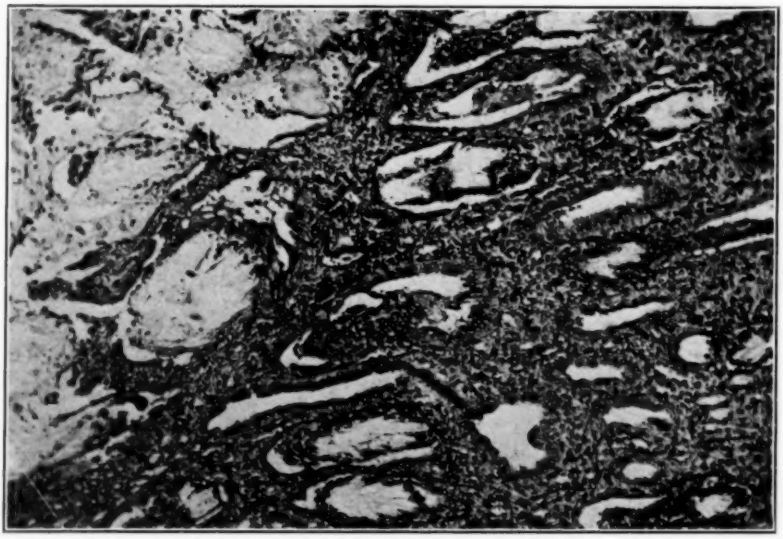

Fig. 3.—Monkey No. 1998. Photomicrograph showing dilatation of ostia of straight tubules with obstruction by crystalline material and suppurative inflammation reaction. (Hematoxylin-eosin, ×105.)

Animal No. 2118 had generalized edema and a severe degree of positive findings. The pelves of both kidneys were practically filled with crystalline material. Animal No. 2119 had a more advanced stage of anasarca and the same positive findings.

EXPERIMENT VII.—A 10 per cent suspension of sulfapyridine in 50 per cent glucose was injected intravenously in two animals. The amount of the drug given was the same as in previous experiments, i.e., 10 gm. in ten days.

The total number of red blood cells and their hemoglobin content were decreased in one animal; there was an increase of lymphocytes from 47 to 80 per cent in one animal, and clinically, crystals were found in one. At no time were the animals ill.

The autopsy examinations of animals No. 1986 and No. 2106 were negative as regards the urinary tract, except for the microscopic observation that the submucosa of the bladder in No. 2106 was severely hyperemic, edematous, and slightly in-

filtrated with lymphocytes. There was severe hemorrhagic necrosis in both axillary and inguinal regions where frequent punctures had been made to inject the drug.

Animal No. 1986 had a hemorrhage in the parietal peritoneum of the lower part of the abdominal area, a possible slight distention of the right ureter, enlargement of the inguinal lymphatic nodes, and hemorrhages in the inguinal regions due to needle punctures. The lymphocytes of the blood increased from 35 to 57 per cent; the leucocytes decreased from 62 to 36 per cent.

III.

In our computations we classed patients from birth to 30 months as infants, those from 30 months to 10 years as children, and those 10 years or older as adults. The amount of sulfanilamide given to patients at City Hospital, Cleveland, depends upon their weight, and for computation purposes weights above 55 kg. are ignored.[4] For the sake of uniformity, the same weight limit was used in determining sulfapyridine doses.

TABLE IV

RECOMMENDED DOSES FOR INFANTS, CHILDREN, AND ADULTS

	TOTAL DOSE (GM.)	WEIGHT IN POUNDS*	WEIGHT IN KILOGRAMS*	AVERAGE DOSES PER KILOGRAM*
Infants	15.5	6- 30	2.7-13.6	5.7-1.1 gm./kilogram
Children	31.0	30- 60	13.6-27.0	2.2-1.1 gm./kilogram
Adults	52.0	60-121	27.0-55.0	1.9-0.94 gm./kilogram
Monkeys	10.0	6.6	3.0	3.3 gm./kilogram

*Approximate figures.

In the work described above, the dosage given the experimental animal was 3.3 gm./kilogram, a little less than that given to infants of comparable weights ill with pneumonia, but nearly two, and sometimes more than three, times the dose per kilogram recommended for older children and adults. Such doses have produced lesions in the experimental animal, and, in our experience, have caused hematuria and a rise in the B.U.N. in a few infants of comparable weight.

It would be important to know if the smaller amounts used in the case of older children and adults would produce lesions in the experimental animal. It was decided to give monkeys weighing 3 kg. 1.5 gm. of the drug per kilogram, i.e., 4.5 gm. of the drug over the recommended period of fifteen days as follows: first day, 0.9 gm.; second and third days, 0.5 gm.; fourth to sixth days (inclusive), 0.34 gm.; seventh to fifteenth days (inclusive), 0.17 gm. (See Table III.) This dose would be slightly less than that now recommended for younger infants and children, but more than that given adults.

EXPERIMENT VIII.—Animal No. 2108 was given sulfapyridine. The urinary bladder was distended 2 cm. above the symphysis pubis but contained only about 0.5 c.c. of clear yellow urine. This seems incongruous, and we have no explanation for this fact. The kidneys were not enlarged; the pelves and ureters were not dilated, and no concretions were found. Four submucous hemorrhages were found in the bladder. (This organ had been manually compressed to obtain a pre-mortem

urine specimen, so that these hemorrhages might possibly have been due to trauma.) There was a slight drop in the total number of red blood cells, the circulating lymphocytes increased from 40 to 80 per cent, and the polymorphonuclear leucocytes decreased from 53 to 16 per cent.

Animal No. 2109, given sulfapyridine and ammonium chloride by stomach tube, became ill after the first administration of these drugs. After the second ingestion, the respirations stopped, and the animal became unconscious and flaccid. It was revived temporarily by artificial respiration, but remained flaccid and died three hours later. This sudden effect was probably due to the large quantity of ammonium chloride given, rather than to the sulfapyridine itself. The autopsy was negative.

Animal No. 2122 was given sulfapyridine and lesser amounts of ammonium chloride. It did not develop any clinical symptoms. The autopsy was negative save for a slight dilatation of the right ureter.

Animal No. 2110, given sulfapyridine and potassium citrate by mouth, had negative clinical findings. The autopsy was negative save for some slight dilatation of the ureters. The lungs contained parasites.

Animal No. 2112, given sodium sulfapyridine by mouth, died twelve days after the experiment was started. There was a drop in both the total number of red blood cells and their hemoglobin content, an increase in the total number of white blood cells, and definite B.U.N. retention. This animal had an increase in lymphocytes at the start of the experiment. The urinary bladder was tremendously distended, extending 6 cm. above the symphysis pubis, and it contained 51 c.c. of urine. There were hemorrhages in the tissues about this organ and inflammatory adhesions between the bladder and abdominal walls, as well as between it and the surrounding organs. The mucosa of the bladder was thickened and hyperemic, and there were multiple hemorrhages and a deposit of fine yellow crystals over its surface. Both ureters were greatly distended and contained large amounts of fine crystals, the left having more than the right. The kidneys themselves were not enlarged, but the pelvis of the left kidney was dilated and contained crystalline material. The pelvis of the right kidney was but slightly dilated. The adrenals and spleen were enlarged.

Animal No. 2111 was given sulfapyridine in glucose by mouth. The entire biliary system, including the common bile ducts and the gall bladder, was considerably dilated and filled with bile, but neither concretions nor obstructions were found. The urinary bladder had a few submucous petechiae and contained only a few drops of urine. The pelves of the kidneys and ureters were not dilated; the kidneys were not distended, and no concretions were found.

Animal No. 2121 was given sulfapyridine in glucose by vein. There was extensive edema of the external genitals. The other positive findings were parasites in the lungs, edema of the peritoneal serosa, and subcutaneous hemorrhages in the right and left inguinal regions due to needling. No inflammation was noted, and the femoral vessels were patent in this area.

IV.

When *M. malatta* monkeys are given doses of sulfapyridine slightly less than that recommended for infants of comparable weight, there may be a decrease in the total number of red blood cells and their hemoglobin content, an increase in the total number of white blood cells, occasionally a reversal of the leucocyte-lymphocyte ratio, and an increase in the blood urea nitrogen.

The toxic reactions seen in these animals were due in part to the formation of concretions in the straight tubules of the kidney in the pelves, ureters, or bladder, with obstruction to the urinary outflow; in part to consequent infections of the urinary tract; and in part probably to an immediate toxic effect of the drug in the epithelium of the convoluted tubules. The same condition has been described as occurring in rats[5-8] and rabbits.[9]

Clinically, lesions in the genitourinary tract were first indicated by finding red blood cells in the urine. Sometimes white blood cells were later seen in the urine, or these cells would appear first and would constitute the only pathologic element found.

In the few experiments performed, sodium sulfapyridine was found to be more toxic when it was used in doses comparable to those recommended for sulfapyridine. A similar conclusion was reached by Molitor.[10] Further experimentation would be necessary to determine

Fig. 4.—Photograph showing concretions in bladder of monkey No. 1974.

if smaller doses of this drug would consistently cause a more prompt and a higher rise in the sulfapyridine level.

Large amounts of fluid did not prevent the formation of stones under the conditions of our experiments. When red blood cells are found in the urine of human patients, it is thought that fluids should be increased cautiously, especially in the presence of edema. Once the latter condition is present, one may infer that there is obstruction somewhere in the urinary tract, and, if fluids are forced, it might aggravate rather than alleviate the urinary condition. The most significant indication that there is some pathologic condition present in either the kidney, ureter, or the bladder which blocks the outflow of urine is the finding of an increase in the blood urea nitrogen.

Two of the animals given ammonium chloride had no lesions of the urinary tract. However, the clinical use of this drug cannot be recommended on such sparse evidence.

It is interesting to note that 10 per cent sulfapyridine in 50 per cent glucose did not cause the formation of urinary crystals, although hematuria was present in one of the animals. This form of administration of the drug did not make the animals ill, but it must be pointed out that it did not produce appreciable blood sulfapyridine levels, even when large doses were used. It may be that the combination of sulfapyridine and glucose may prevent absorption or a breakdown of the former. If this be true, the blood level of sulfapyridine may be misleading. The exact nature of the calculi was not determined. Gross, Cooper, and Lewis have found that the crystals in rats contained 6.4 per cent sulfapyridine and 64.1 per cent acetylsulfapyridine.[5]

CONCLUSION

It has been found that the doses of sulfapyridine sometimes recommended for infants produce clinical and pathologic changes in the urinary tracts of *M. malatta* monkeys of comparable weights.

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CHRONIC GAUCHER'S DISEASE

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IN RECENT years considerable interest has been aroused by reports concerning dysfunction of the lipoid metabolism and the reticuloendothelial system. Such a disorder constitutes chronic Gaucher's disease, also known under a variety of synonyms, namely, primary idiopathic splenomegaly, Gaucher's large cell splenomegaly, lipoid cell splenohepatomegaly, and cerebroside lipoidosis. By description it is a comparatively rare familial constitutional disturbance of unknown etiology, characterized by a deposition of complex lipoid compounds, especially kerasin, in various organs. To date, fewer than 150 cases have been reported in medical literature. This comparatively small number of cases reported adds interest to the presentation of the instance that follows.

Fig. 1.—Patient at age of 6 years, 7 months. The spleen is enlarged 17 cm. below the left costal margin, and the liver is enlarged 11 cm. below the right costal margin. There is moderate anemia.

REPORT OF CASE

A. D., white, an only child, aged 5 years, was first seen for an acute cold in February, 1932. During the course of a routine physical examination there was found, upon palpation of the abdomen, a nontender spleen below the left costal margin, which measured 5 cm. (3 fingerbreadths). Apart from a slight pallor of the mucous membrane of the lips, the significance of which was corroborated by a blood count taken a few days later, the patient was at this time asymptomatic. The liver was also enlarged and measured 3 cm. (2 fingerbreadths) below the right costal margin, the right lobe being lower than the left. All these indications—the palpable liver and spleen, the slightly lemon-tinged skin and conjunctivae,

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the mild secondary anemia and leucopenia—suggested, although not excluding other conditions, a possible Gaucher's disease.

As time passed, the splenic mass and liver gradually increased in size, filling the abdomen. An anemia of moderate severity was later replaced by a greatly lowered hemoglobin and red blood cell count. From June, 1935, until that time when the patient was admitted to the hospital for splenectomy (April, 1939), twelve transfusions of citrated whole blood were administered intravenously.

Both parents, the father aged 32 years, the mother 30 years, were living and in good health. Both were Jewish, the father of German parentage, the mother, Polish.

A tonsillectomy had been performed upon the boy at the age of 2½ years, upon which a good recovery followed. He had measles at the age of 7 years. At the age of 8 an acute otitis media was complicated by a right-sided mastoiditis. Again, good recovery followed a simple mastoidectomy, performed by Dr. Henry Dintenfass, which was followed by a blood transfusion.

The child had a keen mentality shown by excellent scholastic ability; he maintained an optimistic cheerful disposition until near the end.

Fig. 2.—Roentgenogram taken of patient May 4, 1933, at age of 6 years, 3 months. An irregular area of density is shown in the right femur in which there are several rarefied areas. The neck is shortened, and there is a definite coxa vara deformity. The similar condensation seen below the greater trochanter on the left side shows no evidence of rarefaction in its central portion nor any evidence of bony deformity. The cartilage in both hip joints and the heads of both femora are entirely normal.

In May, 1933, when 6 years, 3 months old, he complained of a limp. Examination disclosed limited motion in the right hip. The roentgenologic examination (Fig. 2) reported a coxa vara due to what was probably a long-standing osteomyelitis of the neck of the right femur. Knowing the diagnosis to be Gaucher's disease, the roentgenologist looked especially for evidence of bone changes. The spotty demineralization which characterizes the invasion of the bone by Gaucher's cells

was not found with certainty in any area at this time. None of the vertebral bodies showed any evidence of collapse because of demineralization from such cause. However, the Erlenmeyer flask shape of the lower ends of both femora, a very typical finding, was definitely present at that time.

With the institution of complete rest, the patient made a remarkable recovery insofar as the hip symptoms were concerned. In June, 1935, the hip was apparently normal, and the child had no complaints referable to his right side, although the roentgenologic examination at that time showed no change in the appearance of the femoral neck and of the left femoral shaft since the last report.

During the progress of the disease there was no nausea, vomiting, constipation, diarrhea, or melena. There were no symptoms or signs referable to the pulmonary, genitourinary, and nervous systems.

On the other hand, the lymph nodes in the posterior cervical and inguinal regions were slightly enlarged. The pupils were equal and reacted to light and to accommodation. There was a definite yellowish thickening of the conjunctivae of the eyes, particularly at the nasal sides.

Examination of the mouth revealed an extremely pale mucous membrane. The gingivae were firm and markedly anemic in appearance. A slight proliferation of the gum tissue was noted around the upper central teeth (probably due to incomplete eruption). No exudate could be elicited by pressure around any of the gums. At no time during the child's stay in the hospital were any bleeding or petechial spots noticed in the mouth. The hard and the soft palate and the floor of the mouth were entirely negative. The saliva was thin, watery, clear, and not excessive. The teeth were well filled and clean. The upper left permanent lateral was slightly discolored and did not respond to the pulp tester.

Intraoral roentgenographic examination showed a generalized porosity in the mental region. In the premolar mandibular region, well-formed unerupted premolars were noted directly under the deciduous molars. Although most of this area was obscured by the unerupted teeth, there was some evidence of a pseudocystic formation that resembled bone disturbances found elsewhere in the skeleton. The maxillary region showed a generalized bone demineralization. A slight area of rarefaction surrounding the upper left lateral was not to be construed as an infective process but as the result of a generalized systemic disturbance. The lateral jaw films showed changes similar to those seen in the long bones.

The throat was negative, and the tonsils absent. The chest flared at the lower end of the costal cages. The breath sounds were vesicular and the lungs resonant throughout. There were no râles.

The diaphragm was lifted with the respiratory excursions because of the abdominal mass.

The heart showed no enlargement. A faint systolic murmur localized in the mitral area was heard at the fifth interspace, left mammary line.

The abdomen was greatly enlarged, measuring 74 cm. in circumference at its greatest diameter. It was tense and flat to percussion. No ascites was demonstrable. The spleen was greatly enlarged, its lower pole resting at the symphysis pubis. The notch was felt three fingers above the the umbilicus. Diagonally, across the abdomen from the lower margin of the left costal cage to the right iliac crest, the spleen measured 30 cm.

The liver was felt 12 cm. below the right costal cage and measured 23 cm. in width. The edges of both liver and spleen were smooth, firm, and nontender.

There was no edema of the lower extremities.

Thrombocytopenia has been a common finding in Gaucher's disease. During the last two months of the child's illness, his gums bled easily, and the skin of the upper and lower extremities was found to bruise readily. Blood platelet counts were found below normal on two occasions. The first, taken in 1932 soon after

TABLE I

COMPLETE BLOOD COUNTS

DATE	HEMOGLOBIN (%)	WHITE BLOOD CELLS	RED BLOOD CELLS	HEMOGLOBIN (GM.)	COLOR INDEX	POLYMORPHONUCLEAR NEUTROPHILES	SMALL AND LARGE LYMPHOCYTES	MONONUCLEAR LEUCOCYTES AND TRANS.	EOSINOPHILES	BASOPHILES	MONOCYTES	ABNORMAL CELLS	CHARACTER OF ERYTHROCYTES	REMARKS
2/ 2/32	68	3,600	3,250,000	11.0	1.05	36	62				2	Reticulocytes, 1.7%	Normal	
5/15/32	52	3,400	3,590,000	8.4	0.7	53	43				2	None seen	Normal	
11/29/32	59	3,000	2,940,000	9.6	1.0	46	51	3				None seen	Normal	Very slight poikilocytosis
4/10/33	72	4,250	3,740,000	11.6	0.96	42	53	5				None seen	Normal	
7/ 7/33	75	4,050	3,880,000	12.2	0.96	53	44	1			2	1 lymphoblast	Normal	
9/ 6/33	63	5,750	3,390,000	10.2	0.93	32	60				8	None seen	Normal	
1/24/34	54	4,750	3,660,000	8.8	0.73	71	27	2				1 nucleated red cell	Normal	Anisocytosis, poikilocytosis, achromia
4/ 4/34	60	3,600	3,600,000	9.7	0.83	36	60	3	1			None seen	Normal	Anisocytosis, poikilocytosis, achromia
6/18/34	60	4,150	3,670,000	9.8	0.83	48	42	8		2		None seen	Normal	Anisocytosis, achromia

TABLE I—CONT'D

11/21/34	50	4,650	3,970,000	8.2	0.63	36	60	4					Polymorphonuclear neutrophiles; N F F,* 5%; M F,† 30%	Anisocytosis, poikilocytosis, achromia
7/ 1/35	36	5,500	3,150,000	6.0	0.59	23	62	11	2	2		4 nucleated red cells	N F F, 22%; M F, 1%	Anisocytosis, poikilocytosis, polychromia
9/14/35	50	3,200	3,630,000	8.2	0.69	41	51	8				Occasional basophilic stippling	Normal	Anisocytosis, poikilocytosis, polychromia
2/29/36	55.02	2,500	3,380,000	9.0	0.87	20	78					Blast forms, 2%	N F F, 14%; M F, 6%	Polychromasia
2/22/38	32	3,200	2,720,000	5.3	0.59	47	51	2				None seen	Nucleated; red blood cells absent	Anisocytosis (macrocytosis predominating), poikilocytosis
2/ 1/39	28	6,600	2,570,000	4.6	0.54	29	68	2				Myelocyte, 1%	Nucleated; red blood cells absent	Poikilocytosis
4/ 6/39	58	5,100	3,000,000	9.4	0.97	52	48					None seen	Normal	Poikilocytosis
4/17/39	40	18,400	2,500,000	6.6	0.8	84	16					None seen	Normal	Much achromia, poikilocytosis
4/18/39	52	18,000	2,800,000	8.4	0.96	83	17					None seen	Normal	Achromia, poikilocytosis
4/19/39	55	18,400	2,950,000	9.0	0.92	85	14		1			None seen	Normal	Some achromia; occasional nucleated red blood cell
4/21/39	60	19,600	3,100,000	9.8	0.97	74	20					None seen	Normal	

*N F F = Nonfilament forms.
† M F = Mature forms.

the patient came under observation, gave a count of 145,000 per cubic millimeter; the second count, taken upon the patient's admission to the hospital (April 6, 1939), showed 220,000 per cubic millimeter.

The bleeding time taken at the beginning of the child's illness was 4½ minutes (March 4, 1932), and again seven years later (April 6, 1939), was 19 minutes. The blood coagulation time recorded when the patient was first seen (March 14, 1932), was 7½ minutes, as contrasted with the coagulation time of 5 minutes reported April 16, 1939.

The fragility test of the red blood cells indicated that hemolysis was begun at 0.44 per cent and completed at 0.34 per cent.

Twenty blood counts were taken at fairly frequent intervals (Table I). Pick[1] has stated that in Gaucher's disease the neutrophiles at times are reduced in number, while at other times the lymph cells are diminished. The hemoglobin and erythrocyte count fall somewhat later in the course of the ailment. These indications were found in the case reported, i.e., a relative leucopenia, with the neutrophiles and lymphocytes divided almost equally in numbers, and a moderate anemia. Occasionally the neutrophilic polymorphonuclear cells predominated; at other times a relatively higher lymphocytosis seemed to prevail. One occasion (the blood picture taken late in the course of the disease) showed a markedly low hemoglobin (28 per

Fig. 3.—Smear from spleen in Gaucher's disease (punch biopsy) showing typical Gaucher cells with foamy cytoplasm and eccentrically displaced nuclei.

cent). The lowest white blood count was 2500 per centimeter. Again, as the disease progressed, the hemoglobin became reduced (40 to 60 per cent). However, leucocytosis may occur, as was demonstrated in this case by the relative rise in the white blood cells (18,000 to 19,600) noticeable prior to splenectomy. At this time, too, a preponderance of neutrophiles over lymphocytes was observed, the ratio being approximately 4:1. Few abnormal cells were found. These included reticulocytes, an occasional lymphoblast, nucleated red blood cells, and occasionally a few basophilic stippled cells, blast forms, and a myelocyte. The latter findings, however, were inconsistent. Also noted at various times were achromia, polychromia, anisocytosis, and poikilocytosis.

An attempt was made to demonstrate Gaucher's cells in the peripheral blood. Blood smears were treated with the Wright stain and examined by Dr. Irving J. Wolman, but with only negative results.

A splenic puncture (punch biopsy), performed May 25, 1933 (Fig. 3), was reported upon by Dr. Frank W. Konzelmann as follows: "The amount of evidence is small but is highly suggestive of Gaucher's disease. There were present large cells with a granular or foamy cytoplasm."

Since the fat excretion in the stools is not believed to be a reliable index of a disturbance in lipid metabolism, that determination was not carried out.

The blood Wassermann and Kahn reactions were negative on three separate occasions. A blood smear for malarial parasites was negative, as was also the Widal reaction. On examination the urine and stools were found consistently negative. The basal metabolism rate was +35 per cent.

Blood Chemistry.—The nonprotein nitrogen was 42 mg. per 100 c.c., creatinine 1.3 mg. per 100 c.c. The total blood protein was 6.1 per cent. The blood cholesterol varied from 280 mg. per 100 c.c. to 125 mg. per 100 c.c. On one occasion the blood cholesterol rose as high as 320 mg. per 100 c.c.

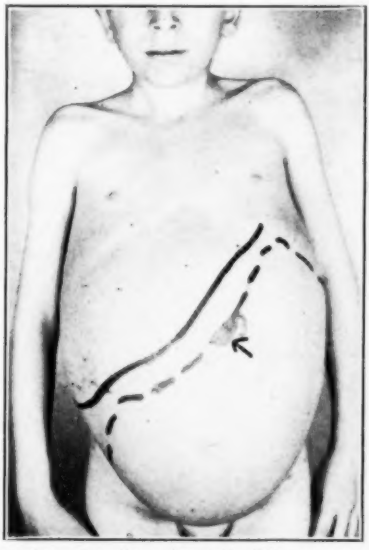

Fig. 4.—Photograph taken of patient April 12, 1939, at age of 12 years, 4 months, two days prior to splenectomy. This shows the enlargement of the liver and spleen; the arrow indicates the splenic notch.

The blood sugar was 96 mg. per 100 c.c.; urea, 18 mg. per 100 c.c.; phosphorus, 4 mg. per 100 c.c.; and calcium, 11 mg. per 100 c.c.

Liver Dysfunction Tests.—It is generally believed that, despite the tremendous enlargement of the liver in Gaucher's disease, the physiologic function of the liver is unimpaired. Accordingly, several liver tests were carried out with this thought in mind. These included: (1) galactose tolerance test, (2) Van den Bergh test, (3) bromsulphalein test, (4) phenolsulphonephthalein test, and (5) cholesterol test.

The galactose tolerance test was found normal. The van den Bergh direct test was negative, the indirect, 0.67 mg. The bromsulphalein showed less than 5 per cent, which was practically normal. The phenol-

sulphonephthalein test showed 95 per cent of the dye eliminated during the first hour, and 25 per cent of the dye eliminated during the second hour.

Epstein[2] has asserted the repeated determination of the cholesterol ester portion of the total cholesterol as a means of determining and following the course of parenchymatous disease of the liver. Such procedure is justified because the esterification of cholesterol is believed to be a function of the liver. Normally 50 to 70 per cent of the total cholesterol is present in the form of ester. Thus the value of the cholesterol in the blood plasma is found to parallel the degree of damage to the liver, decreasing in advanced involvement and increasing with regeneration of the liver. In those terms, no evidence of liver damage was noted in the instant case.

Fig. 5.—Roentgenogram of femora, tibiae, and fibulae taken April 15, 1939, patient aged 12 years, 4 months. Note diffuse expansion of the lower ends of the femora and the mottled oval-shaped areas of decreased density with marked thickening of the cortex and absence of periosteal reaction.

Gaucher's cells have been demonstrated in the kidney parenchyma by Horsley.[3] In the case under study the nonprotein nitrogen was a trifle higher than normal. One cubic centimeter of phenolsulfonephthalein given intravenously resulted in a normal appearance time and rate of excretion of the dye.

For two consecutive days prior to operation the patient received intravenous transfusions of citrated whole blood and normal saline totalling 350 c.c. An additional transfusion of 350 c.c. of citrated whole blood and normal saline was given at the time of operation. Transfusions of 150 c.c. of citrated whole blood and normal saline were continued every second day postoperatively. No reactions followed any of these transfusions until the last one presently to be described.

On April 15, under local and general anesthesia, with the patient lying in the dorsal recumbent position, a 7-inch rectus incision was made and splenectomy performed by Dr. Moses Behrend. The spleen was found enormously enlarged but was not adherent to the abdominal viscera, except where its peritoneal coverings approached the stomach, duodenum, and pancreas. The descending colon was separated from the spleen by sharp dissection, freeing up the parietal peritoneum. The gastrosplenic ligament was divided, and the enormously distended splenic veins were clamped and ligated. A similar procedure was followed with the splenic artery. The spleen was then removed without much difficulty.

There were two accessory spleens, each about the size of a large walnut, which were also removed. Postoperative care was remarkably uneventful except for the catastrophe that occurred on the seventh day following operation, and that, we believe, was precipitated by an intravenous injection of 150 c.c. of citrated whole bank blood. This event will be described in some detail presently.

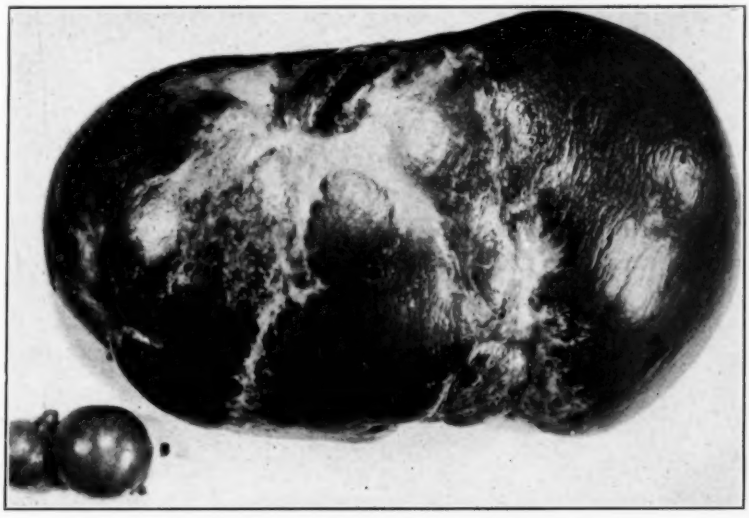

Fig. 6.—Anterior view of spleen photographed upon removal.

The spleen (Fig. 6) measured 22 cm. by 17.5 cm. by 10 cm. and weighed 10½ pounds. The splenic capsule was partly thickened, leathery in consistency, and brownish in color. Large grayish plaques were observed on the outer surfaces. The splenic pulp was soft and red in color. Section of the spleen (Fig. 7) showed extensive infiltration of the sinuses and the lymph follicles by typical Gaucher's cells. The cellular cytoplasm was acidophilic and granular. The nuclei were eccentrically located and circular in shape. Small areas of vacuolization were seen in some of the cells. A number of the cells were elongated and showed signs of cellular compression. Most of the cells were arranged in cluster formation.

As has already been stated, on the seventh day postoperatively, while the patient was receiving an intravenous transfusion of whole blood, he suddenly became apprehensive and complained of a severe pain in the chest. The child said he felt bad and described his sensation as not unlike that experienced by one taking ether anesthesia. He complained that he was "passing out." At the same time the skin of his face and finger tips became cyanotic, the eyes rolled from side to side, and jerking movements of the upper and lower extremities followed in rapid succession. Also, involuntary micturition occurred. Adrenalin (1:1,000) was administered intravenously in dose of 10 minims. A few moments later the patient responded and asked to have his head raised. Then after a few minutes he began shouting. His arms became stiffened, and he made an attempt to bite his feet. Cyanosis became more profound. This was followed in rapid succession by unconsciousness, convulsion, and death. Fifteen minims of adrenalin (1:1,000) administered directly into the heart muscle failed to restore life. Death was believed due to a pulmonary embolism. Autopsy was not performed.

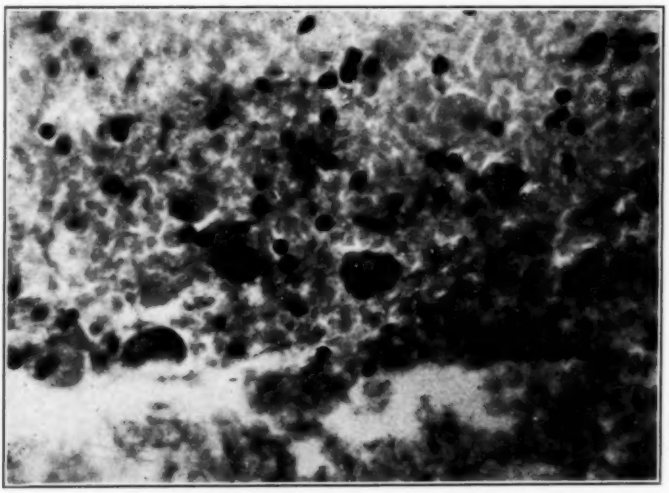

Fig. 7.—Photomicrograph of section of the spleen after removal.

MANAGEMENT

The treatment of Gaucher's disease up to this time has been unsatisfactory, under both conservative and radical regimes. Under the latter, splenectomy has been recommended, either to remove mechanical pressure or possibly to arrest the progress of the disease. Roentgen therapy has also been employed for the latter purpose. However, both surgical intervention and roentgen therapy have failed to accomplish this objective. Furthermore, the high mortality (20 per cent) encountered upon splenectomy emphatically detracts from the merits as an early therapeutic measure.

On the other hand, conservative measures recommend the repeated use of blood transfusions and hematinics. In accord with the suggestion offered by Potter and McCrae,[4] who noticed reduction in the size of the

TABLE II

SUMMARY OF ROENTGENOLOGIC EXAMINATIONS

May 4, 1933	1. Irregular area of density of neck of right femur in which are found several rarefied areas. 2. The neck is shortened. Definite coxa vara deformity. 3. A periosteal reaction along shaft of right femur. 4. A similar condensation seen below the greater trochanter on left side shows no area of rarefaction in its central portion nor any evidence of bony deformity. The cartilages of both hip joints and the heads of both femora are entirely normal. 5. Erlenmeyer flask shape of lower ends of both femora is a very typical finding of Gaucher's disease and is deformity present in this case. Heart and lungs show no significant abnormalities. The skull is normal. There are no abnormalities in the spinal column. The vertebral bodies are of normal stature. Both humeri appear normal. The tibia and fibula of both sides are normal. The feet are not unusual.
Sept. 6, 1933	1. *Comparative Study.*—Little more rarefaction in the neck of right femur than upon previous examination. Slightly more coxa vara deformity. Rarefied area is sharply circumscribed in the neck of the right femur, but is a little longer now than was the case previously. 2. *Interesting Finding.*—In upper part of left femur medullary canal appears to be enlarging at the expense of the cortex; that is, the cortex is becoming thinner and the medullary canal larger since previous examination. 3. *Conclusion.*—Gaucher's disease. Changes in the left femoral shaft can be explained by proliferation of Gaucher's cells in the bone marrow, and this proliferation is probably producing a pressure atrophy of the cortex.
Feb. 14, 1934	1. *Comparative Study.*—No changes in x-ray appearance of right femoral neck and upper portion of left femoral shaft since previous examination.
April 11, 1939	1. The lower ends of both femora present a typical Erlenmeyer flask appearance. There is an infiltration of the medullary cavity which has caused widening of the medullary cavity and absorption of the cortex. This is due to infiltration of Gaucher's cell and not due to an osteomyelitis. There may be a secondary anemia due to bone marrow infiltration. 2. There are numerous transverse trabeculae in a stepladder appearance throughout the shafts of the femora and tibiae, indicating previous growth arrest infections. 3. There is also infiltration of the marrow cavity in the lower ends of the shafts of both humeri, radius, and ulna. There is demineralization with loss of the transverse trabeculae throughout the bones of the hands and wrists. Similar changes exist in both jaws. Bone absorption changes are observed in the ribs. 4. The lung fields are clear. 5. The cardiac silhouette is enlarged. There is moderate hypertrophy of the left ventricle. The aorta is narrowed.

spleen and marked general improvement following parenteral administration of liver extract for nine months,* a similar trial was attempted with our patient.

Three vials of Lilly's liver extract No. 343 in orange juice were employed daily over a period of five years. The extract was well tolerated by the stomach, but no appreciable reduction in the size of the liver or spleen was noticed. The improvement in the anemia was slight. Syrup of ferrous iodide was also administered for three years in doses of 30

*Lilly's Liver Extract No. 343.

minims three times daily at various times over periods of one month without materially affecting the anemia. Eight ounces of freshly prepared juice expressed from the neck of beef were taken daily throughout the entire illness. Other measures employed at one time or another included natural and artificial heliotherapy, the latter from an air-cooled mercury-cooled quartz lamp, and intramuscular injections of iron and ammonium citrate. All these measures resulted in only a temporary improvement of the secondary anemia and were without effect upon the progress of the disease itself.

COMMENT

The insidious onset, the painless progressive enlargement of the spleen and liver, the characteristic roentgenologic appearance of the bones, the moderate to severe progressive secondary anemia, the associated leucopenia, and finally the typical foam cells with eccentrically placed nuclei established a diagnosis of Gaucher's disease.

Interesting was the fact that there was nothing abnormal noticed in the child's health and that he remained comparatively symptomless throughout the course of his entire illness. Despite the enormous size attained by the liver and spleen, the child seemed in apparently good health and enjoyed football and entered into other activities until shortly before his death. Constipation was absent, a daily evacuation of the bowels occurring without resort to laxatives.

It is quite probable that the generalized disturbance of the lipid metabolism which involves the bones interfered with the boy's growth. Reiss and Kato[5] state that cases of extreme degrees of dwarfism and of infantilism associated with mental abnormality have been reported.

Reference to Table III shows that the patient, when first seen, gave height and weight measurements well within normal standards. This age-height-weight ratio continued approximately normal until the age of 9 years was attained, when height and weight began to lag behind normal standards and so continued to fall until a definite disproportion of weight and height to age became evident at the age of 11 years. At the age of 12 years this disproportion had reached a point where there was a 3-inch shortening in height as compared with that of a normal boy of similar age. At this period, too, the patient was 13 pounds underweight.

Cowie and Hoag[6] obtained a maximum rise of blood lipids after five to seven hours in children who had been fed cream after fourteen hours' starvation. In like fashion, Wilson and Hanner[7] found changes in the blood lipids and iodine number in children following the intake of milk containing 40 per cent cream and the ingestion of cod-liver oil. In this study patient determinations were made during fasting and two and four hours later. An increase of the total lipids from 44 to 51.5 per cent was found four hours after the administration of both cream and cod-liver oil. The findings in Pachman's cases[8] were in close agreement with those figures. Bloor[9] reported in dogs, after a fat meal, an increase in the total

TABLE III

DIMENSIONS OF ABDOMEN, LIVER, AND SPLEEN

DATE	AGE	HEIGHT (INCHES)	WEIGHT (POUNDS)	LIVER BELOW COSTAL MARGIN (CM.)	SPLEEN BELOW COSTAL MARGIN (CM.)	MONTHS FROM TIME FIRST SEEN	REMARKS EDGE SPLEEN FELT TO RT. OF MIDLINE ABDOMEN	CIRCUMFERENCE OF ABDOMEN AT UMBILICUS (CM.)
Feb., 1932	5 yr. 2 mo.	42.5	43.5	3.0	5.0	First examination	To left of midline	–
March, 1932	5 yr. 3 mo.	42.5	45.0	7.5	12.0	1	To left of midline	–
Nov., 1932	5 yr. 11 mo.	43.8	45.0	8.0	13.0	9	To left of midline	–
April, 1933	6 yr. 4 mo.	45.0	45.0	10.0	14.0	14	To left of midline	–
July, 1933	6 yr. 7 mo.	45.4	44.25	11.0	17.0	17	Edge spleen at midline abdomen	–
Sept., 1933	6 yr. 9 mo.	45.5	43.0	11.0	17.0	19	2.5 cm. to right of midline	–
Nov., 1933	6 yr. 11 mo.	46.0	44.5	11.0	17.0	21	2.5 cm. to right of midline	–
Jan., 1934	7 yr. 1 mo.	46.2	45.0	11.0	17.75	23	3 cm. to right of midline	–
April, 1934	7 yr. 4 mo.	46.8	48.0	11.0	18.0	26	3.5 cm. to right of midline	–
June, 1934	7 yr. 6 mo.	47.0	49.0	11.0	19.5	28	4 cm. to right of midline	–
Nov., 1934	7 yr. 11 mo.	47.4	51.0	11.0	22.0	33	4 cm. to right of midline	–
July, 1935	8 yr. 7 mo.	48.0	52.5	11.0	23.0	41	5 cm. to right of midline	– 66
Sept., 1935	8 yr. 9 mo.	48.2	52.75	11.0	23.0	44	6 cm. to right of midline	66
March, 1936	9 yr. 3 mo.	49.0	57.0	11.0	24.0	50	6 cm. to right of midline	66
Dec., 1937	11 yr.	51.25	64.0	11.5	26.0	71	9 cm. to right of midline	69
Nov., 1938	11 yr. 11 mo.	51.75	65.0	11.5	26.0	82	9 cm. to right of midline	73
April, 12, 1939	12 yr. 4 mo.	52	64.0	12.0	30.0	87	9 cm. to right of midline*	74

*On April 12, 1939, the liver area from right to left was 23 cm. The spleen from left costal margin diagonally to right iliac crest measured 30 cm.; it filled the entire abdomen.

fatty acids from an initial value of approximately 520 mg. to 620 mg. in two hours, to 880 mg. in four hours, and a fall of 680 mg. in six hours.

In the same experiment he reported that phosphatides, before a test meal being 340 mg., rose to 380 mg. in two hours, to 550 mg. in four hours, and then fell to 450 mg. in six hours. The cholesterol value was 200 mg. before the test meal, remained at 200 mg. in two hours, rose to 220 mg. in four hours, and remained at the latter figure at the end of six hours. In the present case the total lipids,* phospholipids, neutral fat, and phosphorus were within normal limits (Table IV). Cholesterol, the

*The blood chemistry studies were carried out by Dr. David R. Meranze.

cholesterol esters and phosphatase, were decreased below the standard values. Low cholesterol values are not infrequently found in children subject to Gaucher's disease.

Therefore, in order to determine the curve of the blood lipids after the ingestion of a substance high in saturated fatty acids (5 gm. of fat per kilogram of body weight), 500 c.c. of milk containing 20 per cent cream was administered to the patient by mouth after a fourteen-hour period of starvation. A specimen of blood was taken for examination during the fasting period and again at intervals of two, four, and six hours after the test meal.

TABLE IV

BLOOD CHEMISTRY (4/12/39)

	TOTAL LIPIDS (MG.)	PHOSPHOLIPIDS (MG.)	FATTY ACIDS (MG.)	SERUM LIPASE (C.C.)	PHOSPHORUS (MG.)	PHOSPHATASE (BODANSKY) (UNITS)	CHOLESTEROL (BLOOD) (MG.)	CHOLESTEROL ESTERS (MG.)	CHOLESTEROL ESTER RATIO (%)	NEUTRAL FAT
Fasting specimen	333	115	258	0.38	5.52	1.2	75	26	35	143
Second hour specimen	333	115	258	0.45	4.56	1.6	75	25	33	143
Fourth hour specimen	343	138	262	0.52	4.56	1.6	81	27	33	124
Sixth hour specimen	428	148	346	0.60	4.54	1.7	82	29	35	198

For results there was no rise in total lipids after two hours, an increase of 3.3 per cent after four hours. The maximum rise of 28.8 per cent occurred six hours after the test meal. There was only a slight change in the cholesterol values, i.e., they remained unchanged after the first two hours, but increased by 5.6 per cent at the end of four hours, and 6.7 per cent at the end of six hours. No change in the fatty acids was found after two hours, and practically no change after four hours. However, a 34.1 per cent increase occurred after six hours.

SUMMARY

A case of Gaucher's disease is reported in a white boy of Jewish race. Changes in the blood, bones, and spleen have been demonstrated. Normal blood lipoid values were obtained, as well as the normal values for calcium and phosphorus. On the other hand, the cholesterol esters and phosphatase values were decreased.

The ingestion of milk containing 20 per cent cream was followed by a normal fat tolerance curve.

The galactose tolerance test and bromsulphalein test gave normal responses. The phenolsulphonephthalein test showed a normal rate of excretion.

Liver extract administered by mouth over a five-year period, as well as other measures enumerated, failed to cause a reduction in the size of the liver and spleen and resulted in only a temporary improvement in the secondary anemia.

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CONGENITAL CYSTIC DILATATION OF A SINGLE KIDNEY CALIX

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ALTHOUGH congenital anomalies are apt to be multiple, the exhibition of four unusual anomalies of the genitourinary tract, including congenital cystic dilatation of a single kidney calix, presents a rare picture. This anomaly has apparently not been previously reported.

W. L., a male infant, aged 9 days, was brought to the Children's Hospital by Dr. L. D. Buchanan on April 11, 1937, because of fever, vomiting, and abdominal distention. The infant had been delivered spontaneously at term, but appeared to be quite weak and had a poor color. Urine was voided six hours after birth. About this time a fusiform swelling was noted in the ventral surface of the penis, increasing the diameter about twofold. During the next few days it was noted that "he always cried and seemed to strain when he urinated." Urine always came as a dribble, and the dilatation seemed to increase when the baby tried to urinate. The meatus was pinpoint in size, not admitting a small metal probe. On account of the obvious dysuria Dr. Buchanan circumcised the baby on the fifth day and also performed a meatotomy. A number 8 F. soft catheter could then be easily introduced into the dilated portion of the urethra.

For the next three days the infant was in fair condition and gained 2 oz., but on the ninth day abdominal distention, vomiting, and fever caused admission to the hospital. The temperature was 102.5° F. (39.1° C.), skin mottled, pulse weak and rapid, abdomen very distended, and the penis presented a fusiform swelling or dilatation in the middle third. Enlargement of the scrotum was also noted. Laboratory data included a total leucocyte count of 17,400 with 57 per cent polymorphonuclears; red blood cells, 4,500,000, and hemoglobin, 85 per cent (Dare). The urine contained albumin 2+ and 25 pus cells per high power field. Unfortunately, no blood chemical studies were made. A presumptive diagnosis of congenital urethral obstruction and hydronephrosis was made, and parenteral fluids were administered by phleboclysis. Death occurred forty-eight hours after admission.

AUTOPSY PROTOCOL

The body, on external examination, was that of a fairly well-developed and fairly well-nourished white male child eleven days of age. The umbilical cord was dry, ligated, and still attached. In the right ankle region, there was a superficial skin incision.

During internal examination approximately 10 c.c. of clear colorless fluid was found in the right chest, but none in the left chest. Both lungs were dark, congested, and edematous, but with no areas of consolidation. Pericardium, heart, and large vessels were essentially negative.

No free fluid was encountered in the abdominal cavity. A prominent mass was felt in each kidney region. The one on the right side was about the size of a goose egg, and the one on the left side, about the size of a hen's egg. On delivery these structures proved to be the kidneys. In the process of removal, a large

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*Deceased.

cystic structure of the right kidney burst and emptied a considerable amount of clear colorless fluid. On further examination, it was noted that the right kidney was smaller than usual in size, considerably atrophied, and showed fetal lobulation. Attached to the posterior surface of the kidney there was a cystic mass somewhat larger than the kidney itself. On cross section, it was found that this cystic mass (Fig. 1.) communicated with the kidney pelvis and represented an extruded and greatly dilated calix of that kidney. This dilated calix penetrated beyond the kidney cortex and formed the cystic mass, the walls of which were comprised entirely of the wall of the kidney pelvis. The cyst was parallel with the longitudinal axis of the kidney and attached to the kidney only through the anterior wall of the cyst. The communicating opening between the lumen of the cyst and the pelvic cavity was a small round opening measuring 12 mm. in diameter. The main portion of the kidney pelvis, as well as all other calices, showed only a very slight dilatation, and the corresponding ureter was moderately distended and the walls appeared considerably thickened. The left kidney was markedly enlarged

Fig. 1.—Right kidney. *A*, Cyst; *B*, communicating opening between kidney pelvis and lumen of cyst; *C*, kidney pelvis and valvelike fold in ureter orifice at pelvic outlet.

and edematous, and upon the removal of the true capsule, the entire kidney cortex was found mottled with innumerable small abscesses, occurring, for the most part, in large conglomerations (Fig. 2.). Many of the abscess cavities were opened simply by stripping the capsule off the cortex and the outer surfaces of the cortical abscesses were clearly perceptible, that part of the wall being firmly attached to the inner surface of the capsule. The entire kidney substance was edematous, hemorrhagic, and mottled with the above-described minute abscesses. The kidney pelvis was somewhat dilated, and the pelvis, as well as the calices, contained soft, friable, mushy, fibrinous exudate. At the outlet of the kidney pelvis at the upper orifice of the ureter, there was a marked constriction of that orifice. However, below the point of obstruction, the lumen of the ureter remained, not only patent, but also considerably enlarged. The entire wall of the ureter on that side was firm, hard, and indurated. Exploration of the lower urinary passages proved that no anomaly

existed at the bladder orifices of the ureters which were patent and admitted the probing instrument freely. The urinary bladder was somewhat larger than usual, and the wall was enormously thickened and hypertrophied, the average diameter being 4 mm. In the trigon, there was a small edematous and hemorrhagic area, but all other portions of the bladder mucosa were essentially negative. At the internal orifice of the urethra, a large valve was encountered which projected into the urethral lumen downward and anteriorly, terminating in a small knob about the size of a head of a black pin and large enough to produce a complete anatomic, even if not functional, obliteration of the urethral outlet. A probe could pass the obstruction, if inserted from the bladder towards the external meatus, but it could not be probed in the retrograde direction. Below the obstructive valve that was described previously, no anatomic obstruction of the urethral passage could be demonstrated. The exploration of the other abdominal viscera yielded no significant gross anatomic changes.

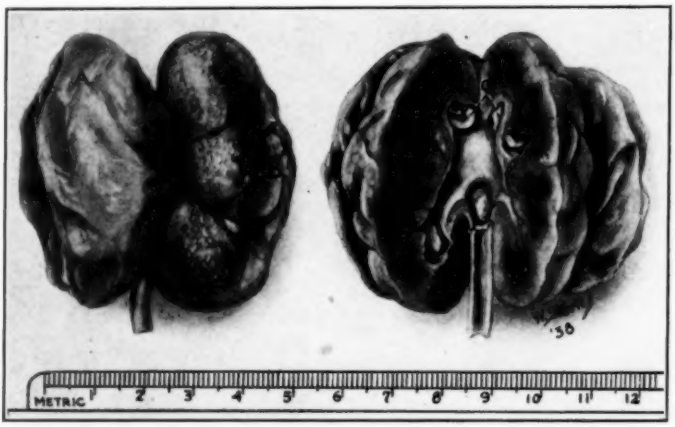

Fig. 2.—Left kidney. *A*, True capsule of kidney folded back, exposing cortical surface; *B*, mottling indicates the multiple abscesses between capsule and cortex; *C*, concretions in calices.

Anatomical Diagnoses.—Congenital malformation of right kidney. Disseminated, purulent, focal interstitial nephritis of the left kidney. Constriction of the left ureteropelvic junction. Congenital valve in the posterior urethra. Hypertrophy of the wall of the urinary bladder.

COMMENT

To the anatomic diagnoses found at autopsy must be added the pinpoint meatus which had caused fusiform swelling of the penis and which had been corrected surgically before admission. The two points of obstruction distal to the bladder accounted for the bladder hypertrophy. These lesions plus the congenital obstruction at the left ureteropelvic junction accounted for the hydronephrosis and multiple abscesses found in the left kidney. The congenital cystic dilatation of a calix of the right kidney was obviously not the cause of death. This anomaly is not to be confused with solitary cyst of the kidney, a relatively rare anomaly. Campbell[1] found five cases, an incidence ratio of 1:2,400. The

right kidney was involved four times, and it is interesting to note that other congenital anomalies were present in four of the five cases. Since solitary cyst is a parenchymal lesion we may assume that the etiology differs from our case.

SUMMARY

A newborn infant died as the result of acute, disseminated, purulent, focal, interstitial nephritis of the left kidney.

Congenital anomolies noted were: (1) congenital phimosis causing fusiform swelling of the penis and bladder hypertrophy; (2) congenital valvelike obstruction in the posterior urethra; (3) congenital constriction at the left ureteropelvic junction, and (4) congenital cystic dilatation of a single calix of the right kidney. Apparently, the latter anomaly has not been previously reported.

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THYROID DEFICIENCY IN TWINS

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DEFICIENCY in thyroid gland secretion presents characteristic mental and physical retardation and functional nonendocrine system reactions frequently attributed to other causes.

A congenital thyroid-deficient child theoretically labels the mother as thyroid-deficient, at least during pregnancy. Most mothers who have given birth to hypothyroid infants have normal thyroid glands before conception and after the birth of the child. A thyroid failure occurs during pregnancy due to the added burden of the embryo. However, after the child is born, the thyroid gland quickly regains normalcy, due to the relief of the incumbrance. Such a mother can be called a potential thyroid-deficient. She may have a failure of the thyroid gland with one child and then produce several normal children; or a mother may bear

Fig. 1.—Case 1. Identical twins, one normal and the other congenitally thyroid-deficient.

several normal children and then produce a thyroid-deficient child. As a rule, it can be said that the continual wear and tear of frequent pregnancies can cause a gradual breakdown of the endocrine apparatus, resulting in a thyroid-deficient state. When twins are born to a potential thyroid-deficient mother, we can naturally expect that such a burden on the thyroid gland will more likely lead to a deficiency than when the pregnancy is single.

A thyroid-deficient child is sometimes not recognized before puberty. If it happens to be of the infrequent obese type, it is usually recognized, but if it is of the more prevalent nonobese variety, the thyroid condition may not be suspected.

Because of the late mental and physical development that occurs in the thyroid-deficient infant, it is often labeled by one of many diagnoses, such as cerebral injury, rickets, scurvy, syphilis, myotonia, or idiocy.

Fortunately, such conditions can be differentiated from the thyroid-deficient state by the fact that a late appearance of the epiphyses and ossifying centers is found only in the latter.

Fig. 2.—Case 1. Normal epiphyseal development.

Fig. 3.—Case 1. Late appearance of epiphyses.

In this report I wish to present cases of three sets of twins, one twin of each set presenting a typical deficient state. I am especially interested in the problem of twins, as I realize that there is often a deficiency in one of a pair of twins. This deficiency may be taken as a natural course of events which cannot be remedied, with the excuse that one twin suffered at the expense of the other.

CASE 1.—The patient, 9 years of age, was one of identical twins. He was retarded mentally and physically so that he approximated the development of a child 6 years old. The other twin was a well-developed boy, with mental and physical

development corresponding to his age. His developmental history was normal. (Fig. 1.)

The patient's developmental history stated that he held his head up at 1 year of age, had his first tooth at 1 year, sat alone at 2 years, stood alone at 4 years, and walked at 5 years of age.

The roentgenologic study showed the following: The os calcis of the ankle was absent (normally appears the ninth year); the proximal epiphysis of the radius was present, but small (normally appears fifth year); the trochlea and olecranon were missing (normally appear ninth year); seven undersized carpal bones were present in the wrist (normally appear sixth year); in the hip the ischium and pubis were separated (fusing normally occurs seventh year); epiphyses of the greater trochanter of the femur were present, but small (normally appear fourth year). The roentgenologic examination of the normal twin revealed a normal appearance of the epiphyses and centers of ossification. (Figs. 2 and 3.)

The diagnosis based on the epiphyseal studies was congenital hypothyroidism. The patient showed remarkable improvement on thyroid extract. His tolerant dose was 6 grains daily.

Fig. 4.—Case 2. Fraternal twins.

CASE 2.—The patient, 2 years of age, was one of fraternal twins. He was retarded mentally and physically. He held his head up at 10 months of age, sat alone at 1 year, and at 2 years of age he could stand only with support and could not walk at all. Mentally and physically he was about 1 year old.

The twin, female, was of normal mental and physical development for a 2-year-old child. (Fig. 4.)

The roentgenologic study of the patient revealed: four tarsal bones present in the ankle (normally appear first year); distal epiphysis of fibula absent (normally appears second year); epiphyses of metacarpals and phalanges absent (normally appear third year). The roentgenologic study of the normal child showed normal appearance of the epiphyses and centers of ossification (Figs. 5 and 6).

The diagnosis was congenital thyroid deficiency. Treatment with thyroid resulted in immediate improvement. The patient died of pneumonia, however, a few months later.

CASE 3.—The patient was 10 months old and one of fraternal twins. She was late in mental and physical development. At the present age of 10 months she

Fig. 5.—Case 2. Normal appearance of epiphyses.

Fig. 6.—Case 2. Later appearance of epiphyses.

Fig. 7.—Case 3. Fraternal twins.

cannot hold her head erect, cannot sit alone, and will not voluntarily reach for objects. The twin has the mental and physical development of a normal 10-month-old child. (Fig. 7.)

The roentgenologic study showed the following: three tarsal bones present in the ankle (appear at birth); distal epiphysis of tibia absent (normally appears first year); no carpal bones present in the wrist (two carpal bones normally appear at six or eight months). The epiphyseal development of the normal twin was proper. The diagnosis made on the patient was that of congenital hypothyroidism, and she responded immediately to thyroid extract.

This report is offered to stimulate further the study of epiphyseal development in questionable cases of mental and physical deficiency.

I especially wish to stress an endocrinologic study of all twins where one of the twins shows some deviation from the mental and physical normal.

A CABINET CUBICLE FOR INFANTS, COMBINING ISOLATION WITH CONTROL OF TEMPERATURE AND HUMIDITY

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THERE is described herein a completely enclosed cubicle with an individual air supply from outdoors heated and humidified as desired. This cubicle, termed a "cabinet cubicle," is a further development of the previously described incubator for premature infants.[1]

On hospitals wards cross-infection among infants and children is a serious problem. The sources of cross-infection are three: (1) actual contact with a contaminated person or object; (2) droplets of moisture expelled from the respiratory tract of such a person; and (3) microorganisms floating in the air. Formerly aseptic techniques have been directed against the first two only. This last source is one which only recently has received attention.[2] It has become obvious that the floating, or air-borne, organisms cannot be disregarded. It is not assumed that the cross-infection prevalent on children's wards is due entirely to them, but it may be stated that they play an important role.

In the course of studies at the Children's Hospital of Philadelphia it was found that bacterial counts on the ward air in the winter months showed 400 to 2,000 colonies of bacteria per 5 cubic feet of air. The wide variation was dependent upon the amount of ventilation present. Each culture without exception, obtained by means of a Wells air centrifuge, had *Streptococcus viridans* colonies which are considered an index of human pollution. Maternity nurseries, maintaining contagious precautions, had considerably lower total numbers of bacteria in the air, but the number of *Streptococcus viridans* colonies was as great. For comparison, outdoor air had fewer than thirty-five colonies per 5 cubic feet, and in no culture was *Streptococcus viridans* found nor any other pathogenic microorganism.

Various solutions to the problem of cross-infection in infant wards have been offered. Incomplete walls between the beds, plus gown and mask technique for the nurses, have proved inadequate. Recently ultraviolet ray "walls" or "barriers" have been installed in several institutions. These barriers would appear especially useful for older infants and children, but rigid isolation technique for the hospital personnel is still required.

For more than two years incubators, described elsewhere, which combine isolation and air conditioning, have been used for premature in-

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fants in various hospitals. Clinical experience with more than 200 premature infants has been most encouraging, for, despite the fact that incubators are used on infected wards, no baby inside one has developed a respiratory tract infection. Infants in them have no contact with ward air, as the air in the incubators is drawn from outdoors and the chambers themselves are never opened. Elaborate contagious precautions are not necessary. The nurse wears no gown nor mask and must be careful only to wash her hands before inserting them into the sleeves through which the infant is handled. Additionally, the temperature control is such that the babies are left naked, and their diurnal temperature fluctuations are usually less than 0.4° F. Their environmental humidity can be controlled very closely, and additional oxygen can be supplied and maintained at any concentration.

Fig. 1.—Outdoor air, after being heated and humidified, passes through the inlet duct, *A*, down behind the headboard, *G*, to enter the cubicle at *I*. It circulates behind the footboard, *H*, to pass over the patient and is withdrawn into the outlet duct, *B*, from which it is exhausted outdoors. *C*, Top window; *D*, back window through which infant in adjacent cubicle is visible; *E* and *F*, doors of air-lock; *J*, cupboard.

It seemed desirable to combine these same principles of isolation and air conditioning for other than premature infants. To this end it appeared essential to protect newborn and weak infants from polluted ward air and to protect the ward air from the infected older infants. These purposes are accomplished in the present cabinet cubicles. These are individual units, each consisting of an airtight chamber enclosing a mattress of crib size. The cabinet has windows on the front and back, permitting excellent vision and light. On the front of the cabinet are the airtight sleeves through which the patient is handled. These are

easily and safely changed, as a second pair can be installed while the first is still in place. In the upper right corner is a large air-lock through which food and supplies are passed. The inside door of this opens down to serve as a shelf or table from which older children are fed. The cubicles are protected against fluctuations in temperature by a system of alarm bells. Air to the cubicle, as to the incubator, is drawn through a duct from outdoors. It is filtered, cooled and dehumidified, and then heated and humidified to any desired level. It follows a common duct from which separate smaller ducts lead to each chamber. The air enters below the mattress, and after circulating beyond the foot of the bed, passes up across the child and is withdrawn at the top into the common outlet duct, which is exhausted again outdoors, above and several feet

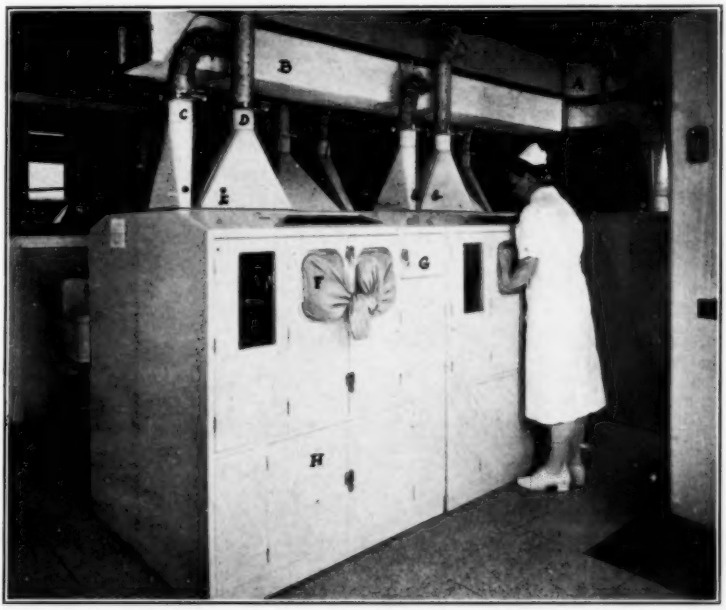

Fig. 2.—*A*, Outlet duct; *B*, inlet duct (insulated); *C*, inlet duct to individual cubicle; *D*, outlet duct from individual cubicle; *E*, petcocks for sampling of the air, or for adding oxygen; *F*, airtight sleeves; *G*, outside air-lock door; *H*, cupboard.
This view shows four cubicles, back to back. In this experimental arrangement the common ducts, *A* and *B*, are above. In linear arrangement they would be concealed in the cupboard space, *H*. The conditioning unit, at the right of the nurse, is capable of supplying forty cubicles.

away from the incoming-air duct. It is possible to select for the group of cubicles any degree of temperature and percentage of relative humidity. Arbitrarily, 82° F. and 40 per cent relative humidity have been chosen for winter. There are petcocks in both inlet and outlet ducts for bacterial sampling of the air with the Wells air centrifuge, or for addition of oxygen. Both ducts have valves so that either the incoming or the outgoing circulation can be stopped. The valve on the outlet duct

is closed when the doors of the cubicle are opened for weighing or treating an uninfected baby. The closing of the outlet duct causes an increase in the positive pressure within the cubicle, and thus, when the doors are opened, the air blows outward, minimizing the entrance of room air into the chamber. When the doors are open, the mattress and spring can be pulled out 12 inches to facilitate bed making and examination or treatment of the baby. Direct ultraviolet irradiation of the air around the infant may be carried out during such times in a manner similar to the irradiation of air in operating rooms.[3]

Because of the wide range of atmospheric conditions possible in the cubicles, they can function efficiently as pneumonia tents, with low temperature and low humidity; as croup tents with moderate temperature and high humidity; as shock beds with high temperature and high humidity; as well as for purposes requiring less extreme conditions.

Another advantage in this type of cubicle lies in its economy of floor space. Each infant in a cabinet cubicle has as much room as in the old glass-walled type of cubicle. On the other hand, the space for the nurses' equipment is eliminated. It would be possible, therefore, by actual measurement at the Children's Hospital of Philadelphia to convert a 16-bed ward, 51 by 29 feet, with glass-walled cubicles into a 67-bed ward of cabinet cubicles, with the present allowance of 5 and 7 foot aisles. For maternity nurseries, small cubicles of a similar type can be used.

An interesting observation has been made concerning infants placed in the cabinet cubicles. A number of them who had been crying constantly on the ward became placid when in the cubicles. It is impossible to know whether this result was due to the moist air and constant temperature or to the removal of the extraneous disturbances and noise.

Bacterial counts taken from the air as it entered the cubicles proved to be lower than those taken outdoors, and in neither have *Streptococcus* viridans nor pathogenic microorganisms been found. In the air leaving the cubicles those bacteria contributed by the patient are detected.

TABLE I

BACTERIAL COUNTS

DATE	SAMPLES	AVERAGE COUNT PER 5 CU. FT. OF AIR	REMARKS
Outdoor Air			
3/16/39	5	8.2	Mostly molds and sarcinae
4/19/39	6	11.2	Mostly molds and sarcinae
Air at the Inlet Ducts Following Filtration			
2/27/39	3	3.6	Mostly molds and sarcinae
2/29/39	7	1.0	Mostly molds and sarcinae
3/ 1/39	7	2.1	Mostly molds and sarcinae
3/16/39	10	1.8	Mostly molds and sarcinae
3/17/39	7	1.3	Mostly molds and sarcinae

TABLE II

AIR AT THE OUTLET DUCTS

DATE	SAMPLES	DIAGNOSIS	AVERAGE COUNT PER 5 CU. FT. OF AIR	REMARKS
3/21/39	6	Bronchitis	9.3	12 colonies hemolytic staphylococci
3/22/39	9	Cleft palate and harelip	10.6	19 colonies hemolytic staphylococci 6 colonies *Streptococcus viridans*
3/23/39	3	Cleft palate and harelip	20.3	11 colonies hemolytic staphylococci
4/ 1/39	5	Otitis media and bronchopneumonia	120.3	91 colonies hemolytic staphylococci 3 colonies *Streptococcus viridans*
4/13/39	12	Cleft palate and harelip	13.5	8 colonies hemolytic staphylococci 6 colonies *Streptococcus viridans* 3 molds
4/26/39	5	Diarrhea	55.0	30 colonies hemolytic staphylococci; child crying hard
4/26/39	8	Malnutrition	3.0	1 colony hemolytic staphylococci 1 mold; child very quiet

In these cabinet cubicles the patients are comfortable, nursing care is facilitated, and floor space is conserved. Of primary significance, however, are the facts that contact infection is minimized, droplet infection is excluded, and air-borne infection is eliminated.

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PSYCHOLOGIC CARE OF THE PRESCHOOL CHILD

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PART II

D. Training
- Bowel and vesicle
- Eating
- Sleeping
- Dressing, undressing, washing
- Sex information
- Property rights

E. Discipline

F. Disturbances of training
- Eating, anorexia, etc.
- Sleeping
- Enuresis and fecal incontinence

G. Undesirable habits
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- Nose-picking
- Masturbation
- Lying
- Stealing

D. TRAINING

DURING the period of emerging self-dependence the child is developmentally ready to acquire a large number of techniques such as self-feeding, self-washing, undressing, dressing, regulation of bowels and bladder, etc. Training during this period is facilitated by certain characteristics of the young child such as suggestibility, imitativeness, and love of praise and applause. By making his skills habitual, the child is freed early in life from the necessity of thinking about routine procedures.

Proper timing is of the utmost importance for the success of training procedures. Because of the wide variability in the tempo of psychologic maturation, the chronologic age is in itself an unreliable index of the degree of readiness, and reliance must be placed on clinical observation of the individual child. The optimal time to train a child is when he indicates a desire to be trained. Training procedures, introduced

From the Children's Medical Service, Bellevue Hospital and the Department of Pediatrics, New York University, and the New York Infirmary for Women and Children.

prematurely, are not only ineffective but may be actually harmful. Parental disappointment at the child's failure to live up to expectation leads to parent-child conflict and may give the child a sense of anxiety, inadequacy and defeat.

There is danger also in retardation. Failure to permit the child to exercise his emerging potentialities represents a developmental delay, and the child consequently remains psychologically immature and infantile.

Bowel Training.—By the end of the first year bowel training is fairly well established in most infants although it is necessarily incomplete since the child cannot be expected to take responsibility for the act much before the middle of the second year.

Vesicle training may be started about 11 or 12 months of age. The best time to start training is when the child begins to show evidence that he is aware of bladder distention by whimpering, pulling at the diaper, or restlessness. Most children may be trained for vesicle control by the second birthday but lapses frequently occur. These should be approached calmly by the parent. Picking the child up at night is not of great benefit in training during the second year. The child should be able to take full responsibility for toilet regulation by the third birthday.

Eating.—By 12 to 18 months most children can manage the cup easily and have some facility with the spoon. Many children of 2½ years can use a fork fairly efficiently. The fork should be light, short-handled and sufficiently sharp to grasp food. If the child is taught that it is sharp, there is little danger that he will hurt himself. At 3 or 4 years the child may use a dull knife for spreading butter on bread.

The socially accepted methods of eating may be taught after two years. Even earlier, however, the child should be discouraged from eating with his fingers. The opportunity to see adults eat, with an occasional suggestion, is ordinarily sufficient and much more effective than interference and constant correction.

Sleeping.—From 18 months to 2 years twelve hours' sleep each night and one sleeping period of one and one-half to three hours during the day are usually sufficient. The daily nap should be continued until the fifth year. Children who rebel against the day nap should be made to understand that sleep is not essential and that resting is as important as sleeping.

The time for sleeping should be definite and exceptions not permitted. The child should be warned a few moments before bedtime so that he may have time to finish what he is doing. After the child is in bed, the light should be extinguished, the door closed, and the child left alone. If possible, the sleeping room should be sufficiently isolated so that sounds from the living room will not be heard, as they may stimulate the child's interest and excite his curiosity.

It is advisable to have a period of quiet play or a quiet story before bedtime so that the child will be relaxed and calm. He should be put on the toilet, given a drink of water if he is accustomed to it, and the complete routine carefully carried out so that there will be no excuse to get up later because something has been forgotten.

It is preferable for the child to have his own room, or, if necessary, to share it with a sibling of the same sex. After 5 years it is inadvisable for children of different sexes to share a room. Children should not sleep in the same room with a sibling who is approaching puberty or is adolescent.

Dressing and Undressing.—At about one year many infants can remove their stockings and hats. By 2 years most children can take off all their clothes except sweaters and tight garments going over the head. At 3 years the child should be able to undress and dress himself entirely except for bows, back buttons, and tight clothing.

Children should be encouraged to undress and dress themselves. As soon as they can walk easily, they may be taught to assist at putting their clothes away, and hooks should be provided for this purpose. Most children are quite willing to accept this routine if they are not hurried, and many enjoy it. A reminder to keep going or an occasional word of encouragement is helpful, but dressing should be accepted as a matter of course, and the child should not be praised or too much attention paid to his achievement. Parental patience will be rewarded by the child's ability to take care of himself.

Washing.—Children can be taught to wash themselves fairly efficiently by 2 years, brush the teeth a little later, and by 4 years they should be able to bathe themselves entirely and brush their hair fairly well. With a gentle reminder from the mother these procedures readily become routine and discussion about them with the child is avoided. Some overprotective mothers take pleasure in washing their children, and it is not unusual to see older children continue to be bathed by their mothers.

Sex Information.—The child's interest in sex varies with age, and it is erroneous for the parent to interpret it in adult terms. Young children ask about the source of the excreta, the possession of the penis, differences in the sex organs, nudity. The parent should avoid any show of disgust at the child's questions and should reassure him and help him to accept his own sex role. Young children are content with a very small amount of information. A child's sex questions should be answered in good faith whenever they are asked, and information will be accepted in whatever spirit it is given. When questions are not asked, it is usually because the child senses parental shyness.

Parents should recognize situations in which instruction may be given naturally and easily just as it is given in other fields. Situations need not be invented nor knowledge forced. Most children ask ques-

tions relative to sex at about 4 or 5 years and continue, if not discouraged, up to 10 years, after which there is a decline. There is no need to find parallels in flower and animal life; if the comparison is at hand and suitable, it may be used, but usually the deviation from the question asked is obvious and makes the child uncomfortable. The answers should include more than an attempt to intellectualize the process by a biologic description of conception, pregnancy, and birth. These form only a small part of the wisdom and insight which children need in order to fit them for full and mature sex life. More important to the child's security and development is for him to feel that he has, in his parents, two human beings who love each other as equals and are partners in their marriage enterprise.

Property Rights.—A respect for the property rights of others should be taught at an early age. As soon as the child is able to walk, he may be told not to touch certain things as they belong to someone else who does not wish to have them disturbed. As he grows older, arrangements should be made for the child to have some place of his own where his privacy will be respected.

E. DISCIPLINE

Permitting the child an outlet for his developing skills and feelings does not mean that he is to be indulged without limit. To hold or rock the child all the time is hardly conducive to the training of a well-balanced personality. Such conduct only sharpens the demands of the child and leads to an egocentricity which is highly undesirable.

Training and discipline are implements used to direct the child's energies into acceptable channels, to assist him in outgrowing less mature modes of behavior, and to curb excessive emotional demands. Training implies active encouragement; discipline implies restraint.

Disciplinary action, in order to justify itself, must serve a useful purpose and should not be made an outlet for the disciplinarian's offended sense of dignity or an emotional release for the parent. The relationship between parent and child must not be jeopardized by the method of discipline, and the parent should avoid vindictiveness or resentment. So far as discipline involves frustration or deprivation, it is important that it be made emotionally acceptable to the child by giving adequate reassurance of affection and concern.

The desires of young children often run counter to the precepts and judgments of their parents. Their resistance to commands is not so much a revolt against authority as an effort to carry out their own plans without interruption or interference. The child must be permitted to experiment and to act on his own initiative to the extent that he is intellectually capable, but his conclusions should be reasonably controlled. He should have increasing freedom as his legitimate needs and capacities grow, but this freedom must be limited by his ability

to take responsibility. He must be told the reasons for restrictions and the consequences which might result. He should be urged to use his own judgment wherever possible, but this cannot be done without direction and guidance. Turning the child loose does not make him independent. Authority which is firm, kind, reasonable, and consistent gives the child that sense of security which is essential for his emotional development since it defines for him the limits beyond which he may not exert his independence. Parental hesitation and discussion often lead to negativism. In the administration of disciplinary measures a sense of humor in both parent and child is invaluable.

Too much self-control must not be expected of a young child. He must be protected against temptations until he has matured to the stage where he can be expected to resist them. So, also, he must not be asked to make promises. He is incapable of remembering directions for long periods of time, and often, if he forgets and breaks his promise, he is scolded both for disobeying originally and for not keeping his promise. A young child does not comprehend the meaning of honor or trustworthiness.

After the third or fourth year it is usually possible to reason with a child, but it is undesirable to establish the custom of prolonged discussions over misbehavior. Too many children enjoy the added attention obtained in this way and so continue the discussion beyond all reason. Silence on the part of the parent will often gain the point when talking is an obstruction. There is little use in trying to reason with a child immediately after he has been punished, and it is valueless to insist on repentance, because, when forced, it is seldom sincere. It is often preferable to let the child "save his face."

Ordinarily a first offense should be punished if the child realized it was wrong. Punishment involves pain and, to be effective, the pain inflicted must be greater than the pleasure derived from a given act. When the punishment is over, the entire matter should be promptly dismissed, and the child reinstated in the family group. He should not be permitted to feel continued disapproval, as this may give rise to feelings of inadequacy, guilt, or insecurity. If the misdemeanor is again committed, the punishment should be more severe than it was the first time, but there should be no threat of punishment if it is repeated.

Inevitableness and immediateness are the two most important elements in successful punishment. A third is to be sure that the child realizes that the misdemeanor has been balanced by the punishment and that the episode is over and forgotten. Very young children may be punished by a sharply enunciated "no," by a cross look, or by a light slap on the hand. These act as conditioning stimuli just as the loud noise of falling dishes or a burn on the hand from a hot radiator will inhibit the action the next time the child reaches for the table cloth or puts his hand near something hot. If the parent maintains an affec-

tionate, understanding attitude toward the child even while voicing disapproval, there will be little chance that the child will develop feelings of revenge and resentment. For the small child, if pain, discomfort, or disapproval follow almost automatically upon misbehavior, he will soon realize that undesirable behavior brings unpleasant results, and he will therefore learn not to repeat the offense.

After the first 2 or 3 years of life probably the most effective means of punishment are scolding, deprivation of privileges, and isolation. The advantages of these methods are (1) that no physical pain is involved, (2) that the duration and severity of punishment may be varied, (3) that there is not a long period for the child to feel abused and to consider revenge, (4) that when the punishment is over the child may be reinstated in the family circle, and (5) that there is no element of the parents' personal feeling present. The child should be made to understand why the act he committed was undesirable and therefore punishable. Persuasion is a poor method of discipline.

When isolation is used as a punitive measure, it should be made clear to the child that the intent of the punishment is removal from the group because of antisocial behavior. No emphasis should be put on the place where the child is to be isolated, and the parent should never threaten the child with confinement in any particular place. The child should not be kept in his room as this may condition him unpleasantly against a place which he should enjoy and where he should feel freest. Similarly, going to bed should not be used as punishment since resting and sleeping should be made as pleasant as possible, with no unhappy associations. The child should not be isolated in any place where he may be afraid, such as an attic, a lonely room, or a closet, since this may lead to fear of the dark or of being alone or may give him an undesirable emotional shock. He should not be isolated long enough to meditate on methods of revenge. The parent should take the initiative and invite the child to return to the group, assuming that he is going to behave. There should be no threat of desertion by the parents.

Wherever possible there should be some relationship between the type of punishment and the nature of the misdemeanor. Thus it may be pointed out that immature behavior is punished by deprivation of some more grown-up privilege. One must be careful that overseverity does not discourage the child's initiative.

It is important to try to understand the child's point of view, thereby eliminating the possibility of his feeling that he is misunderstood and is punished unjustly. If misbehavior remains unpunished, the child may develop a feeling of guilt and may try to punish himself by hiding in a closet, by hurting himself, or by asking to be spanked.

There are certain situations in which there must be immediate, implicit obedience. These are, for the most part, situations which concern the child's safety. The child should be made to understand what these

situations are and why he should obey at once without question. He can soon learn that a certain tone of voice or a special word from the parent "Stop" or "Be quiet" must be obeyed. This can and should be made automatic.

In our complex society discipline must be used for instilling knowledge of the social amenities and for teaching respect for the property of others. There are many customs which we observe for no reason other than that it is usual to act in a certain way, and there is little point in trying to explain by fabricating reasons. For example, the child soon learns that it is not because he will cut himself that he must not eat with his knife. It is much better to say that there are certain things which are not customarily done, and therefore that the child may not do them. There is no reason for this except that society of which he is a part does not do it. The similarity with certain tabus which children have among themselves may be pointed out. They do not tell on each other, they do not run to mother crying, etc.

A sense of humor and a sense of perspective developed in the child are invaluable. The child's life as a whole should be looked at and discipline should be such as to accomplish what one wishes in the long run. In this way nagging can be avoided and the whole plan of training made clearer to the child. Thus punishment for an unsocial act may be dispensed with if the child understands his guilt and shows an understanding attitude toward what he has done and why it is being handled in a particular way by the parent.

F. DISTURBANCES OF TRAINING

EATING

Anorexia is one of the most frequent complaints for which children are brought to the pediatrist. The symptom is usually psychologic in origin but must be distinguished from poor appetite associated with organic disease. In psychologic anorexia the physical status of the child is usually good and fussiness about food is prominent, certain foods being eaten well one day and refused the next. Milk may be taken from a glass but not from a cup. The appetite is often highly variable, depending on the mood of the child, the person present with the child at mealtime, and the type of entertainment supplied. Where anorexia is due to organic disease, on the other hand, the symptom ordinarily appears fairly abruptly and is general, relating to all the food in the diet. There is usually failure to gain or actually a loss of weight, and apathy and easy fatigability are frequently associated symptoms.

Specific food dislikes are sometimes associated with food sensitivity (e.g., dislike of egg in egg-sensitive children), and in such instances the food dislikes should be respected and substitutes offered.

In many children about whom the parents complain of anorexia, there is actually no loss of appetite but a refusal of the child to eat

what the parent wants him to eat. A child may eat with relish certain foods which he likes but refuse to eat foods which the parents feel are good for him.

Though children with anorexia are ordinarily thin, it is by no means unusual to hear this complaint from the parents of children who are actually obese. In some instances the anorexia may be severe and accompanied by marked weight loss.

Etiology.—Psychologic anorexia is observed in all social groups, even the poorest, though it is more common among the economically better situated. It may arise solely as a result of improper management of the eating situation, or it may be part of a generally improper attitude of parent toward child. Anorexia nervosa may have its origin in the parental anxiety about the lack of appetite following an ordinary respiratory infection.

Physiologic Anorexia.—Anorexia usually begins toward the end of the first year or in the second year and continues into the early school years. It may, however, appear as early as the eighth or ninth month of life. Its onset coincides with the beginning of "physiologic anorexia." During the first 9 months of life physical growth is rapid, and the need for food correspondingly large. Toward the end of the first year the rate of physical growth falls off rapidly, continuing at a fairly low level until about the sixth year, at which time an increase in the growth rate begins. During the period of relatively slow growth the need for food is not as great as early in life and the appetite is consequently reduced. Parents, unacquainted with the normal growth cycle, are frequently disturbed by the child's diminishing interest in food and by the slower weight gain, and hence proceed to urge the child to eat. The parental urgings serve to stimulate the child's resistance to authority which is emerging at this age period, as part of the maturation process, and in this way a psychologic factor is added to the physiologic. Furthermore, the child, becoming aware of the parental interest in his diet, may use the eating situation as a means of gaining attention or as a spite mechanism.

Parental Oversolicitude.—The more or less natural train of events just described may become exaggerated under a number of circumstances. One of the most potent causes of anorexia is parental oversolicitude regarding the health of the child. In many parents the normal concern for the child is exaggerated and the emphasis placed on nutrition within the past thirty-five years has served to focus parental interest on this subject. Parental anxiety has been reinforced by the popular use of tables of growth and by a widespread belief that rapid growth is optimal growth. Physicians and social agencies are in no small way responsible for this viewpoint. Parents of the oversolicitous type may go to extremes to induce the child to eat, using bribes, threats, forced feeding, punishments, etc.

Parental Overprotection.—Another factor leading to feeding difficulties in children is an overprotective attitude on the part of the parents. Overprotected children are retarded in the use of the implements for eating as well as in other manifestations of self-dependence. Such children are often infantile in their behavior not only toward feeding but toward other training procedures, particularly self-dressing and self-washing. Feeding difficulties apt to occur in the overprotected child are refusal to give up the bottle, insistence on puréed foods, refusal to chew, refusal to swallow solid food, and insistence upon being fed.

Parental Indifference or Rejection.—The most severe instances of anorexia are seen in the offspring of parents who are emotionally indifferent or actually rejecting in their attitude toward the child. Such parents, because of a sense of duty or because of a feeling of guilt regarding their own attitude, are often overprotective. The child, lacking the affectionate atmosphere necessary for normal personality development, is restive and seeks compensation for his unsatisfactory environment by refusal to eat. In rejected children, the desire for attention is abnormally developed, and feelings of revenge are prominent.

Suggested Food Attitudes.—Though the mother is usually responsible for most feeding difficulties, suggested food attitudes ordinarily come from the father or older children. These suggestions are frequently made unconsciously, and the parent is usually unaware that he is at fault. The most common food attitude suggested is dislike of particular foods. Vomiting, postprandial sense of pressure, or abdominal pain may also be suggested.

Occasional causes of feeding difficulties are anxiety on the part of the child because of parental incompatibility or jealousy of a younger child. Undue excitement before mealtime is another factor.

Prophylaxis.—Anorexia can be easily prevented if proper measures are taken during the first year of life.[19] The pediatrist, seeing the child during early infancy and observing his relation to the parents and often to the grandparents, can usually evaluate the parental attitudes and introduce corrective measures before any effect on the child is apparent. This attitude on the part of the physician, if applied tactfully and early, particularly before difficulties arise, is gratefully accepted by most patients. Special emphasis should be placed on the parental attitude toward the eating situation since it is here that difficulties frequently arise. Before prescribing a feeding schedule for a young infant, some estimate of the maternal psychologic make-up should be made. For the easy-going mother, who might be expected to be lax in following directions, the importance of a rigid schedule should be stressed; for the meticulous, overanxious mother, on the other hand, a strict schedule should be avoided and some leeway as to the hours of feeding and even the amounts to be given at each feeding may be safely advised. For the overanxious mother every attempt should be made to minimize the importance of diet as well as other aspects of the child's training.

During infancy parent-child conflicts regarding foods should be avoided. With the introduction of each new food, the mother should be advised that children differ in their food likes and dislikes. If a food is refused, its preparation should be investigated; if this is found satisfactory and hence not the cause of the child's dislike, the food should be withdrawn and a substitute offered. The particular food may be reintroduced at a later date or in a different form. The parent should be told that no food, except milk, is essential for the child and substitutes can always be found. It should be repeatedly emphasized that even a young infant is entitled to some food likes and dislikes. In recommending new foods, the amounts to be given should be made flexible.

The proper use of height and weight tables should be stressed. The idea that the weights and heights of children fall into a zone of normality rather than along a line may be readily imparted to most parents. It should be pointed out that there is no evidence to indicate that children whose weights are above average are healthier than children below average. The vitamin needs of children are limited, and large supplements are probably of no value and may even be harmful.

Proper training of the child in the use of eating utensils so that he can eat unaided should be stressed.

The feeding time, from early infancy, should be regular but not too rigid and the surroundings pleasant and free from distractions such as toys. The food should be well prepared and served, and the child should be given a choice of foods. Small portions should be served, and the child should not always be required to eat everything put before him. Voicing of food dislikes by elders should be avoided.

Treatment.—Before instituting treatment a proper appraisal of the psychologic environment should be attempted. Severe feeding difficulties are much less likely to arise in happy children than in those poorly adjusted. An effort should be made to differentiate the various parental attitudes, normal parental anxiety, overanxiety, overprotection, indifference, and rejection. Parental incompatibility or sibling rivalry should be investigated. Where severe anorexia is present, parental rejection should be suspected and treatment directed toward this situation. A general survey of the child's behavior should also be made.

In mild cases of anorexia, disregard of the symptom together with an explanation to the parent of the limited dietary needs of the child during the preschool period is often sufficient for cure. The child should receive attention and affection when he behaves, not when he misbehaves.

Miniature meals are sometimes sufficient to change the child's attitude from one of distaste to one of desire for food. This is more especially so when food has been forced or too large helpings have been served. A choice of foods, or the elimination of foods which are customarily refused, may increase the appetite.

Excitement and vigorous exercise should be avoided before meals. A child should have sufficient warning before mealtime so that he can complete what he is doing and hence will not resent eating because it is taking him away from incompleted play. Also the desire to get back to his play will not be so great if it has not been left unfinished.

Having the child eat with other children is often helpful.

Dawdling over food, as well as dawdling in general, is the child's negativistic reaction to parental, sibling, or nurse overauthority. Whenever this symptom is encountered, the child's attitude toward dressing, his response to requests, as well as the parental attitude should be investigated, and the parents instructed accordingly. Dawdlers should eat alone, and, after an adequate time has been allowed for eating, the food should be removed without comment. Dawdling over meals may occur when the child is bored with the daily routine or when there is a disagreeable task to be performed. It must be distinguished from slow eating which is usually due to poor training but may have some other basis not completely understood. In some children this can be corrected by an explanation of the social advantages of more rapid eating, but it occasionally persists throughout life.

Refusal to Chew.—Some children either refuse to chew or chew weakly and expectorate solid particles. The food may be retained in the mouth for long periods. This is an infantile reaction and occurs most often in the overprotected child. In such instances the parent-child relations should be discussed with the parent. Solid foods which the child is known to enjoy should be offered. The child should be given the opportunity of eating with children of his own age, e.g., at a nursery school.

Insistence on being fed is another infantile manifestation and should be treated like refusal to chew.

Vomiting is an uncommon symptom during the preschool period. There are occasional children who vomit readily when exposed to various situations, e.g., when urged to eat, when excited or when riding in cars, at the onset of infection, etc. This type of response unquestionably has a psychogenic component but probably, as in the case of enuresis and stuttering, there is also a neurogenic basis as indicated by the familial occurrence and the persistence throughout life. Cyclic vomiting also has a psychogenic component and attacks are frequently precipitated by birthday parties, holidays, and other exciting events.

Since vomiting may be a manifestation of organic disease, a careful investigation should be made in every child with this symptom. Allergy is a factor occasionally, and in such instances the vomiting is accompanied by refusal of the offending food. Egg is the food most commonly implicated. The identification of a food with a disagreeable object or situation may lead to vomiting. Vomiting is occasionally utilized as an attention getting or spite mechanism. It may be suggested by a parent

or sibling. An attempt should be made to discover and correct the underlying maladjustments. Phenobarbital is a helpful adjuvant in treatment.

Pica or Perverted Appetite.—Pica usually develops in the second or third year of life. The child may eat paint, soot, chalk, dirt, plaster, or paper or may chew bed linen, wool, or clothes. Indeed, there are few things which such children will not eat.

Ordinarily the symptom is innocuous but it may give rise to serious disturbances. The eating of paint may lead to lead poisoning. Hairball tumors have been known to cause intestinal obstruction. Since the symptom usually occurs in neglected children, the patients are frequently thin and pale and suffer from gastrointestinal disturbances of various sorts.

Pica occurs most frequently in low grade mentally defective children and may persist throughout life. It is seen, however, in children with normal mentality. It results from inadequate supervision and can usually be cured by proper training, if necessary away from home. Normal children after the ninth or tenth month put objects into the mouth indiscriminately. Persistence of the symptom in children of normal intelligence after the fourth year of life is of grave prognostic significance and is usually associated with other deep-seated behavior disturbances.[20]

SLEEPING

Sleep disturbances occur most frequently after 3 or 4 years of age. There may be difficulty in falling asleep, crying at night, frequent waking during the night, restless sleep, and unwillingness to go to sleep.

Physical factors such as pain or discomfort (e.g., ammoniacal dermatitis), hunger or thirst, inadequate coverings, poor ventilation, or abdominal distention may interfere with sleep.

Faulty training is the most common cause of sleep disturbances during the preschool period. The symptom is rarely an isolated one and usually accompanies other training difficulties, particularly eating. Improperly trained, overindulged children often insist that their parents go through a ritual with them at bedtime. They may require their parents to lie down with them until they are asleep or insist on being put to bed in the parents' bed; others will not sleep without a light, while still others dawdle about going to bed, getting up several times to do something which has been forgotten. These maneuvers may represent a real desire to remain awake, or they may be simply a method of obtaining attention.

Restless, hyperactive, excitable children frequently suffer from sleep disturbances. If the mind is crowded with ideas, sleep will be delayed and when it comes it may be restless and unsound. Overexcitement may result from overstimulation with dancing lessons, drawing lessons, exciting school activities or from active play immediately before bedtime.

Secret Practice of a Habit.—Some children remain awake at night in order to practice in secret habits which are not permitted during the day, such as nail-biting, thumb-sucking, and masturbation.

Emotional Disturbances.—If there have been difficulties and misunderstandings during the day, the child may lie awake at night to ponder his problems. Sleep means relaxation and the cessation of mental and physical activity, and one cannot rest when emotionally disturbed. Some children remain awake to plot revenge for assumed or real injustice or because they are concerned about their conduct.

Conditioning the child against his sleeping room or against being left alone may lead to sleep disturbances. Being put to bed or shut in one's room as a punishment is likely to cause dislike of that particular place.

Fear.—Children who have not been trained to assume responsibility may be afraid of being left alone at night because during the day they have not been accustomed to being by themselves and have not been taught how to act if something unforeseen should happen. Darkness, creaky beds, slipping covers, or shadows may frighten an imaginative child. Even adults sometimes suffer from this. Stories of hobgoblins and bogy men intensify this fear and should never be told to children. Nowadays it is more common for children to be afraid of burglars and kidnapers because of the radio or discussion of newspaper stories in their presence.

Suggested Sleep Disturbances.—Sleep disturbances in children may be unwittingly suggested by adults. Casual remarks regarding one's inability to fall asleep or what a poor night one has had may appeal to the child as attractive adult attitudes, and he may try to acquire them himself, thus fighting off sleep.

Curiosity may lead to wakefulness. Adult conversation in the child's presence may stimulate his interest and curiosity, thus preventing sleep. If the child shares a room with his parents or sleeps near by and has had opportunity to observe the sexual act, he may remain awake in order to see more or to ponder what he has already seen. This may lead to disturbing dreams, sleep walking, and night terrors. After weaning, the infant should not share a room with his parents.

Treatment.—The treatment of sleep disturbances necessitates first the correction of the underlying mechanism and second a discussion with the parent of the proper attitude toward sleep. The amount of sleep necessary varies with the individual, and actually rest is almost as important as sleep. The parent should approach the problem without undue concern.

For the child with a sleep disturbance overstimulation and undue excitement before bedtime should be avoided. In a hyperactive child a warm bath followed by a pleasant story may be soothing. If there have been difficulties or misunderstandings with the child during the day, these should be discussed and adjusted before bedtime. Even if the child cannot explain the reason for his unhappiness, the parent should comfort

him and assure him of his worthiness. Children with habits which they practice in bed should be given sufficient exercise and a shorter rest period during the day so that they will be more likely to fall asleep immediately upon being put to bed. A sedative for a few days may aid in breaking the habit of lying awake.

Faulty training for sleep is usually a manifestation of poor general training. The entire situation must be reviewed with the parent and a plan laid down for establishing a better routine. The sleep rituals should be discontinued, and the child made to understand that he is expected to remain in bed and that no amount of crying will aid him. During the period of training bromide or phenobarbital may be of benefit.

Nightmares and night terrors are fright reactions during sleep. In the case of the nightmare the child awakens in terror from a dream usually characterized by a feeling of suffocation and helplessness. He can ordinarily relate his bad dream, can recognize people about him, and can be readily calmed. Nightmares are often very vivid and the recollection of them, accompanied by a sense of dread, sometimes recurs during the following day when the child is awake. They are not uncommon and occur most frequently within an hour or two after going to bed.

Night terrors are relatively rare. They differ from the nightmare in that the child does not awaken fully and has no recollection of the incident. The child is usually found sitting up in bed or standing or running about, greatly agitated, and screaming. There are frequently hallucinations of strange people or animals in the room. The child is disoriented and does not recognize persons about him. The attacks subside after several minutes, the child dropping off to sleep without remembering the episode. At times it is necessary to awaken the child before the attack subsides.

Some children seem especially prone to night terrors, and they may be repeated three or four times a month with restless nights in the interim. In other children they occur only once or recur only at long intervals. There appears to be no direct association between night terrors and other sleep disturbances; but all are seen most frequently in children who are emotionally unstable and who tend to be anxious.

Sleep-talking.—Talking during sleep is not uncommon in young children. Most speech is mumbled and unintelligible. Often the child calls only the mother's name or addresses some remark to her. Sometimes the child speaks of his waking experiences. Occasionally a wish is expressed probably related to the dream the child is having. The child may call out in sleep and appear frightened, or he may become so upset that he cries and screams as in the case of night terrors.

If the cause of the sleep disturbance can be determined, it should be corrected. The child's environment should be adjusted so that there will

be no factors present which may disturb sleep. There should be no excitement or rough play before bedtime. If there has been some misunderstanding or emotional disturbance, this should be cleared up.

Somnambulism or sleepwalking is rare before adolescence. In the young child it is usually directed toward the parents' room and may be an attempt to satisfy curiosity about the sexual act or a desire to share the mother's bed. It is possible that the child is seeking in fantasy what he cannot have in reality. As with adult somnambulists some children do constructive things, others destructive and foolish. Excellent mental and muscular correlation enables them to walk fearlessly upon precarious ledges. These episodes usually end happily, but there have been numerous deaths of sleepwalkers. To awaken a somnambulist when he is in a precarious position is dangerous as it may upset the coordination between mental and muscular activity.

The child usually is unaware that he has been out of his bed and even when awakened during his walking cannot describe what has happened. Some sleepwalkers speak with great facility and can carry on a conversation.

Treatment.—As in related disturbances the environment should be adjusted. A satisfactory explanation should be given to the child's curiosity about sex. If there is excessive fearfulness, the cause should be eliminated; if jealousy, a more satisfactory familial relationship should be established.

DREAMS

Children's dreams are simple and are the result of past experience or are wish-fulfillment dreams. The age at which the child first dreams is not known, as language ability is necessary for the dream to be related. Presumably dreaming occurs before the child can tell of it. Children recount their first dreams at about two years. They generally say, "Last night I thought," or, "While I was asleep I saw," etc. The first dreams are not necessarily realistic. "Last night a lamb slept with me" is typical of an early, related dream. The young child has difficulty in separating dreaming from actuality. His powers of description are limited and he will frequently fill in "gaps" and reject absurdities in his dreams which are contrary to his actual experience.

Enuresis, day wetting, and soiling have been discussed in a previous paper.[21]

G. UNDESIRABLE HABITS

Thumb-sucking.—The habit of thumb-sucking, once established, usually persists into the preschool period. There may be associated movements such as ear pulling, lip-stroking, head-patting, hair-pulling, etc. The habit ordinarily disappears spontaneously when the child is 5 or 6 years old but may persist into adult life. Usually the thumb is sucked only at night or at nap time or when the child is tired, sleepy, bored, or

sulky. In some instances the bedclothes may be drawn over the face while the child sucks the thumb.

Thumb-sucking is a useless activity which deflects a considerable amount of energy from other channels. It is an infantile act and represents a developmental delay. The child's awareness of the undesirability of his act may lead to a feeling of inferiority, sense of guilt, and to secretiveness.

Treatment.—Where thumb-sucking occurs only when the child is tired or sleepy, special treatment is unnecessary and may be actually harmful. If, however, the habit is frequently practiced during waking hours it means that the child is bored or unhappy and hence an investigation of the unsuitable psychologic environment should be made and corrective measures attempted. A sense of responsibility and a feeling of usefulness should be given to the child when possible. The parents should be warned against shaming and nagging.

The basis of treatment is the substitution of useful and pleasant activities such as toys and games for the thumb-sucking. Mechanical restraints are useless and may produce results more harmful than the original habit. Material rewards are seldom successful.

By 5 years of age most children are capable of understanding the disadvantages of thumb-sucking. They may be told that the habit is infantile and that being grown-up implies being able to conquer the habit. Responsibility in other fields sometimes increases the feeling of assurance that this habit may be stopped. At times a direct appeal to the child's will power may be made and a simple chart constructed to show objectively how improvement is taking place day by day. Some children are impressed by an appeal to their vanity and stop this unpleasant habit almost at once. If a reminder is needed, the child may apply a bitter substance to the thumb.

Tongue-sucking is relatively uncommon. It is seen occasionally in infants who are prevented from sucking the thumb, in Mongolian idiots and cretins, presumably because of the macroglossia, and occasionally in otherwise healthy infants. The tongue may be inserted into the cheek and moved about, it may be rolled up and moved up and down against the palate, or it may be moved backward and forward between the lips (particularly in Mongolian idiots and cretins). It is often accompanied by a loud sucking sound and infants seem to derive great satisfaction from this practice. The habit is harmless and usually disappears spontaneously during the second year of life although it occasionally persists for a longer time.

Tongue-sucking in a thumb-sucker who has been restrained may be cured, if the infant is seen early enough, by removing mechanical restraints and offering a pacifier. Later lollipops may be used, and efforts may be made to distract and amuse the child with toys.

Nail-biting is one of the most frequently observed undesirable habits in childhood and adult life. It usually begins in the fourth year of life, occasionally earlier or later. Ordinarily, several members of the family are nail-biters, and the child acquires the habit through imitation. It is most commonly seen in tense, excitable children in contrast to thumb-sucking, which is more likely to occur in children who are outwardly calm and placid. The habit is likely to be practiced in situations associated with repressed excitement and secretly, if the child has been made to realize that the habit is undesirable.

Nail-biting is occasionally associated with biting of the toenails and with picking at the nails with the fingers. Kanner[22] finds that biting of the toenails occurs almost exclusively in girls, and this has also been our experience.

The treatment of nail-biting is ordinarily unsatisfactory. Punishments, scolding, and restraints are of no value and may, as in the treatment of thumb-sucking, lead to other psychologic difficulties. Since nail-biting, like thumb-sucking, is more likely to be practiced in an unsatisfactory psychologic environment, attempts should be made to relieve existing tensions in the home. Sometimes the child may be urged to save one nail—meanwhile biting the others if necessary. When the one nail is long, that may be sufficient incentive for the child to stop biting the nails entirely and to let all grow long. Light cotton mittens worn at night may act as a reminder that the nails are not to be bitten and pajamas which encase the feet may be used in the same way in toenail-biting. The child may use a bitter substance or adhesive tape on the nails for the same purpose. Rewards are sometimes of value.

Nose-picking is very common in children during the preschool period and the early school years. It is sometimes associated with the unpleasant habit of putting the contents of the nose into the mouth. An appeal to the child to do away with this unpleasant act has more effect here than in the case of most habits. The child usually has some appreciation of the undesirability of his behavior and desires to stop. Having a handkerchief always available and establishing the habit of its use are helpful.

Masturbation[23] may be defined as "the manipulation of the sex organs for the purpose of obtaining a pleasant sensation." It is uncommon before 10 or 11 years of age.

In infants and young children all erogenous zones (mouth, breasts, anal region) are believed to have the same value as sources of pleasure, and masturbation is said to be purely autoerotic with no other object than the infant himself.

Erections occur in infancy, and at times may be coincidental with or due to manipulation of the sex organs. When this occurs, it may lead to further exploration because of curiosity or interest. It is to be

regarded with concern only when it becomes habitual. Erections are frequently seen in infants just before micturition.

Sometimes nursemaids or parents induce the habit of masturbation by stroking the child's thighs. This causes a pleasurable sensation and often soothes the child, and is therefore continued. Usually this is done without the appreciation by the adult of possible consequences. Tight clothing or other irritation of the external genitals may lead to handling of the sex organs and subsequently to masturbation. Even such innocent acts as sliding down a pole or swinging may produce sensations leading to further investigation and manipulation of the genitalia. Masturbation is only rarely taught by older children to a child under school age.

The untoward consequences of masturbation are for the most part due to poor management of the situation by the parents. It is now known that no mental or physical disturbance, other than local irritation, can result from masturbation per se. When it is known that a child masturbates, it is most important to assure the family and the child that there is nothing inherently wrong in the act and that it is usually temporary and without serious consequences. In the small child it is often sufficient to tell him that this is an infantile habit which he is too old to continue. It is most important that the child should not become ashamed and so resort to secrecy, as this is where the most distressing result appears.

The exciting factor should be eliminated and any local irritation corrected. An outlet for the child's excess energy should be provided, and his time should be fully occupied. A regular daily regime with plenty of exercise and wholesome social contacts is a great aid in overcoming the habit.

Opportunities for masturbation should be avoided, small children being taught to sleep with their hands outside the covers. Small boys may wear trousers without pockets, and it is well to avoid such toys as hobby horses and swings. Various types of mechanical restraints have been tried. They are useless and often harmful. The only successful approach is through a moral and intellectual understanding of the child.

The emotionally unsatisfactory life, so often a factor in adolescent masturbation, has little meaning in the preschool period.

Lying.—Willing falsification of facts is uncommon before the fifth year of life. It is only as children grow older that they learn the advantages of lying.

Fantasying is not uncommon in young children. The child fabricates from the love of yarning or to escape from a real world that he finds dull or disagreeable. The fancies and make-believe of childhood arise through confusion between reality and fantasy and are free from malice. The young child sees so little logic or reason in most actions that it seems to him that anything may happen. He hears Mother Goose tales and fairy stories, and consequently his world is one where fancy and fact are confused.

It may be desirable to encourage this quality, thereby stimulating the imaginative faculty. It is not harmful if the child is made to realize from time to time that these fancies are the products of his own imagination; and corrective measures need be taken only when fantasying is carried to an extreme and the child lives too much in an imaginary world.

Treatment.—Excessive fantasying can be readily overcome if the child's attention is directed to the difference between fancy and reality by asking whether the tale is real or make-believe. Simply saying "That's make-believe, isn't it?" is usually sufficient for this purpose. If the child fantasies to free himself from a world which is either uninteresting or unpleasant, this should be corrected. The interesting aspects of everyday objects should be emphasized and stories told about real happenings in the world.

Stealing is rare before school age, but many children during the fourth and fifth years acquire pencils, toys, and useless objects which do not belong to them. Such behavior is best prevented by teaching the child, through word and example, respect for the property of others. Arrangements should be made so that the child may have some place of his own for his belongings such as toys, clothes, etc., without interference from other members of his family. In this way he will soon learn to appreciate and care for his possessions and will be more respectful of the rights of others.

(To be continued.)

Critical Review

VITAMIN K FOR THE PEDIATRICIAN

With Special Reference to Physiologic Hypoprothrombinemia of Newborn Infants

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IN THE past few months there has been brought to the attention of the public a new vitamin to which fabulous cures have already been ascribed. Ever on the alert, the physician must acquaint himself with the substance, its consequences when withheld from the diet, and its effects when administered in concentrated form. In only the past few months the use of the vitamin K has been placed at the "doorstep" of the pediatrician, and it now appears that it is his problem as well as that of the general practitioner.

HISTORY

Vitamin K is defined as a specific, fat-soluble substance, the absence of which in the diet of chicks causes the blood to clot slowly.

Although embryonic in its appeal to the public, vitamin K is by no means a new departure. The background of its discovery is as classical as any of the stories of the medical world. In 1929, Henrik Dam,[1] working in the laboratories of the University of Copenhagen, studied the fat metabolism of the chick. During the course of investigation he noticed that chicks fed on a fat-free diet for two or three weeks developed fatal hemorrhages into the muscles, gizzard, and subcutaneous tissues. Further study revealed that the fatal cases had extremely low levels of plasma prothrombin. He believed that there was an unknown substance lacking in this fat-free diet that was essential for the proper coagulation of the chick's blood. And, since the Danish word for clotting is spelled "Koagulation," he named this unknown substance vitamin K.

Coincidentally, Horvath[2] in this country observed that diets of sprouted soy bean would accelerate the clotting of the blood of chickens.

Roderick,[3] working for the United States Government in 1929, was sent out to discover the cause of "sweet clover disease" in cattle. He found that cattle fed on spoiled clover hay were prone to develop fatal hemorrhage during the dehorning process. Examination of the cattle that died revealed a central liver necrosis. He observed further that all cattle that obtained alfalfa in addition did not develop these hemorrhages. In all cases there was an associated low plasma prothrombin of the cattle that died.

At the end of 1931 McFarlane, Graham, and Richardson[4] discovered that chickens fed on a diet containing ether-extracted fish meal suffered from the hemorrhagic tendencies, but that those fed on unextracted fish meal did not suffer the hemorrhages.

From the Children's Hospital, Joseph S. Wall, M.D., chief of staff.

In the summer of 1935 Almquist and Stokstadt[5] confirmed the previous work of Dam and showed that vitamin K deficiency resulted in low prothrombin levels in the blood of the chick. In October Quick, Stanley-Brown, and Bancroft[6] proved conclusively that plasma prothrombin was definitely decreased in persons suffering from obstructive jaundice. In hemophilia the prothrombin was normal.

That vitamin K was synthesized by bacterial action was established by Dam and Schønheyder[7] in the same year. They also showed that vitamin K was to be found in certain green vegetables, such as alfalfa, spinach, and kale, and in hog-liver fat. Fermented fish meal had a large store of the vitamin. In 1936 the first crude concentrated form of vitamin K was prepared by Almquist.[8] He was able to distill and concentrate one kilogram of alfalfa down to 2 mg. of the crude vitamin by the use of a hexane extract.

Since Quick had already called attention to the low prothrombin level in jaundice, Hawkins and Brinkhous[9] undertook to evaluate the prothrombin concentration in dogs after establishing biliary fistulas. They found that the tendency to bleed was directly proportional to the drop in prothrombin and was corrected to a degree by the addition of bile salts to the diet. In rats the same phenomenon was noted.[10] With attention drawn to the fact that vitamin K appeared to be necessary for the formation of prothrombin, it became necessary to determine the source of prothrombin. Smith, Warner, and Brinkhous[11] and Quick[12] in 1937 proved the source of prothrombin to be in liver. By using chloroform they caused a liver necrosis in dogs and were able to simulate the hemorrhage that occurred in "sweet clover disease." Basing his views on these findings, Quick again advocated the use of vitamin K in cases of biliary obstruction about to undergo surgery.

Clinical evidence lent its support when Butt, Snell, and Osterberg[13] successfully demonstrated that postoperative bleeding in gall bladder surgery was minimized by the use of vitamin K. Since then it has become a routine practice to correct preoperatively a low prothrombin concentration by the use of bile salts and vitamin K. Recently it has been found by Almquist and Klose[14] that certain naphthoquinones, chiefly phthiocol which was isolated first from the tubercle bacillus by Anderson, show some antihemorrhagic properties.

SOURCE, ACTION, AND MODE OF ADMINISTRATION

It is now known that vitamin K is absorbed in the intestinal tract in the presence of normal bile and is then utilized to synthesize prothrombin in the liver. Whether the vitamin is stored in the body is not known, but it is found in the feces of both man and the chicken. It is found in sufficient quantities in the average diet but is not absorbed in an upper intestinal tract in which there is no bile. In obstructions of the biliary passage, bile is prevented from entering the intestinal tract, and vitamin K is not absorbed. The blood prothrombin then drops to low levels, and bleeding occurs very readily. The critical level at which bleeding will occur has been found to be 10 per cent of the normal prothrombin concentration. At 20 per cent the least trauma will initiate bleeding. From 20 to 50 per cent, the decline of prothrombin will occur very rapidly and is dangerous because of postoperative bleeding. Fifty to seventy-five per cent concentration requires investigation because, with any appreciable amount of hemor-

rhage, a further loss of prothrombin will occur. The normal limits are considered to be from 75 to 100 per cent. Although prothrombin can be supplied immediately in the form of whole blood by transfusion, the duration of prothrombin-usability is very short, and it becomes necessary to seek further means to raise the prothrombin level. Vitamin K with bile salts begins to raise a low prothrombin within three to six hours, and one can restore the concentration to normal in less than twenty-four hours.[15]

The source of vitamin K has been determined with fair accuracy, and some claim to have isolated it in pure form. Those substances which contain the antihemorrhagic property in the order of their potency are:

1. Putrefied fish meal.
2. Alfalfa
3. Hog-liver fat
4. Kale
5. Spinach
6. Dried carrot tops
7. Chestnut leaves
8. Tomatoes
9. Oat sprouts
10. Soy bean oil
11. Naphthoquinones

All the above contain varying amounts of the vitamin, but their potency can be increased by allowing them to putrefy. Many microorganisms contain the vitamin, and as previously mentioned, it is produced in varying amounts in the intestinal tract of man. In a recent article Doisy[16] reports a pure extract of vitamin K which he claims was obtained from putrefied fish meat. It is a light yellow, crystalline, solid salt at room temperature. Another compound, obtained from alfalfa, is a light yellow oily liquid at room temperature. Almquist's preparation is a colorless, crystalline, fat-soluble material easily destroyed by heat and sunlight. Commercially it is prepared from a petroleum ether extract of alfalfa and is called "Klotogen." It is marketed in either a peanut- or maize-oil base and is available in liquid or capsule form. At present, it is being prepared for intramuscular use. Another preparation is a powdered cereal known as "Cerophyl." The latest reports deal with the uses of phthiocol intravenously for the administration of vitamin K.

It is rather difficult to standardize a compound of which there is no pure form. However, Dam identified a unit of vitamin K as that amount of vitamin K contained in one gram of dried spinach. Dam has defined a unit as the least amount of vitamin K per gram of a chick's body weight per day which is necessary to prevent a prolongation of the clotting time beyond normal limits. Others have gauged the dosage by the amount of the original alfalfa from which the extract was made. For example, Smith, Ziffren, and Hoffman[17] use vitamin K equal to extracts from 300 to 400 Gm. of alfalfa meal. Peroral administration is the method of choice. It is given either as the oil or the powder in an emulsion of three to four drams of bile salts or other bile preparation three times daily. The intramuscular route has no advantage over the oral route. Phthiocol has recently been reported as being used intravenously with success in cases that require rapid vitamin K therapy. One can gauge the dosage by observing the rate of rise of the prothrombin concen-

tration. An overdose will not provoke any untoward symptoms. Quick believes that "Klotogen" in dram doses every six hours is sufficiently potent. All clinicians are in agreement that vitamin K is most effective when given in conjunction with bile or bile salts.

Because of its expense, it becomes necessary for the physician to know when vitamin K therapy is indicated. It is safe to say that vitamin K is only indicated in those conditions of hemorrhage or potential hemorrhage in which there is a definite hypoprothrombinemia. Prothrombin metabolism is interfered with when:

1. Vitamin K is inadequate in the diet
2. Bile is not present in the upper intestinal tract.
3. Fat digestion is interfered with.
4. Normal mucosa of the upper intestinal tract is destroyed.
5. Liver function is interfered with

When the above conditions are responsible for a hypoprothrombinemia, then vitamin K and bile are indicated.

PROTHROMBIN

The infrequency with which routine blood prothrombin determinations are performed makes it advisable for the clinician to become familiar with the background and essential details of the test. As yet, the exact nature of prothrombin is unknown.[18] It is a protein of complex nature capable of forming an active enzyme known as thrombin. It is closely associated with plasma globulin. It has been isolated as a white amorphous powder insoluble in water and having reactions similar to a metaprotein. It is claimed that 100 c.c. of blood will yield about 40 mg. of this powder. Its origin, previously thought to be in the bone marrow, has recently been proved to be in the liver. Warren and Rhoads[19] observed that, following total hepatectomy in dogs, there was a rapid decline in the plasma prothrombin. A slight fall in the fibrinogen content was also noted. They concluded that prothrombin is synthesized in the liver by the action of vitamin K in the presence of normal bile in the intestinal tract.

When Quick approached the problem of bleeding in jaundice, he discarded all the accepted theories up to that time, most of which claimed either calcium, fibrinogen, or the blood platelets to be faulty, and began a systematic search for the proper answer. Previous to 1935 prothrombin determinations were performed according to Howell's technique, which consisted in timing the formation of a clot by recalcifying the blood plasma. Quick improved the method by adding a tissue extract to insure the complete conversion of all the prothrombin present. He based his observations on the basic theory of blood clotting as put forward by Howell. Briefly, this theory states that in the blood stream are found four agents responsible for the clotting of the blood. These are calcium, fibrinogen, prothrombin, and thromboplastin. Calcium will react with prothrombin to form thrombin which becomes active with fibrinogen to form the insoluble fibrin and resultant clot. However, in the circulating blood is found a substance called heparin which holds the prothrombin in an inactive state. Thromboplastin, also called cephalin, is released by the disintegrating platelets and neutralizes the heparin and thus allows the clotting process to go to completion. It has been shown by Mellanby, Schmitz, Kühl, and Quick that heparin is really an antithrombin rather than an

antiprothrombin because it appears to inactivate the thrombin after it is formed from its precursor. However, this in no way interferes with the determination. The method developed by Smith, Warner and Brinkhous[11] is an elaborate one and not ordinarily suited to the average laboratory, although it may be advocated for research purposes. It consists mainly in timing and measuring the second phase of the clotting process. By the method of Quick, a known excess of thromboplastin is added to a known amount of oxalated serum which contains the unknown prothrombin. Then an excess of calcium solution is quickly added, and the time required for the formation of a clot is noted. In normal blood the rate of the clot formation is an indirect measure of the amount of prothrombin present in the blood. Since it is known that the thromboplastin and calcium solutions are in excess, the only variable becomes the prothrombin because the amount of fibrinogen is negligible. With rabbit brain as a source of thromboplastin, the clot will form in normal blood in from 13 to 15 seconds. With an extract of human brain, the clotting time averages normally about 24 seconds. The delay in the clotting time is directly proportional to the drop in prothrombin concentration. To determine the percentage of prothrombin, Quick has devised a formula:

$$\text{Clotting time} = a + \frac{K}{C}$$

in which C = prothrombin concentration
a = 8.7
K = 330.00

The Quick test is simple enough to be performed by any laboratory and accurate enough to be recognized by laboratories engaged in research on the subject of hemorrhage due to prothrombin deficiencies. Because the proper technique of the test seldom appears in print, it seems advisable to give the materials and procedure necessary for accurate performance.

TECHNIQUE OF TEST FOR PROTHROMBIN DETERMINATION

Solutions required are:

1. Sodium oxalate: 1.34 Gm. of anhydrous pure sodium oxalate are dissolved in 100 c.c. of distilled water.

2. Calcium chloride: 1.11 Gm. of anhydrous, chemically pure calcium chloride are dissolved in 400 c.c. of distilled water.

3. Thromboplastin sol.: Mix 0.3 Gm. of dehydrated rabbit brain with 5.0 c.c. of 0.8 per cent sodium chloride containing 0.1 c.c. of sodium oxalate solution. This mixture is incubated at 45° C. for ten minutes and centrifuged for three minutes to obtain a clear milky supernatant fluid. (The rabbit brain is prepared as follows: the brain is stripped of the pia and is macerated in a mortar and extracted with acetone. The solvent is poured off and more acetone is added, and the process is repeated until a granular powder is obtained. This product is dried at 37° C. and placed in a clean stoppered tube. It retains its activity for a week. Deterioration is much slower in a vacuum tube.)

The quantitative determination is then performed as follows:

Three cubic centimeters of blood are obtained by venipuncture and mixed with 0.3 c.c. of the sodium oxalate sol. and centrifuged. One-tenth cubic centimeter of the clear plasma is mixed with 0.1 c.c. of the thromboplastin sol., and 0.1 c.c. of the calcium sol. is quickly added.

The time required for the clot to form is noted. The normal is between 13 and 15 seconds.

Smith and others[17] have perfected a crude test for the approximate prothrombin determination, which is done as follows:

A thromboplastin solution is prepared by adding 10.0 c.c. of normal saline to each 10.0 Gm. of fresh ox or rabbit lung and grinding this together. It is stirred at intervals for several hours, and the fluid obtained is strained and stored in the refrigerator. One-tenth cubic centimeter of this solution is then drawn up into a serologic pipette and placed in a standard Wassermann tube. Then 1.0 c.c. of freshly drawn patient's blood is placed in the tube, mixed, and the clotting time noted. This is compared with a test on normal blood done at the same time. A rough estimate can thus be obtained by comparison.

DISEASES CHARACTERIZED BY HEMORRHAGE

With the advent of a relatively simple test for prothrombin determination, investigators turned toward other diseases characterized by bleeding tendencies. The majority of these conditions, among which may be mentioned menorrhagia, metrorrhagia, hemophilia, essential thrombopenic purpura, toxic purpura, essential hematuria, Banti's syndrome, uncomplicated hemolytic icterus, familial bleeding tendency, aplastic anemia, and hemorrhagic duodenal ulcer, failed to respond to vitamin K therapy. In a few isolated cases success was reported.[15]

HEMORRHAGIC DISEASE OF THE NEWBORN INFANT

Among the tragedies that befall the newborn infant are the fatal hemorrhages of unknown origin that occur without warning shortly after birth. To these conditions Townsend[20] gave the name hemorrhagic disease of the newborn. The term is loose and vague in its description and until recently has included those hemorrhages of unknown etiology which occurred during the first few days of life after trauma, sepsis, syphilis, and hemophilia had been ruled out. There has been no agreement as to a characteristic pathologic picture. Many have shown that there appeared to be a delayed bleeding and coagulation time during the first few days of life. Although roughly, the disease includes all neonatal hemorrhages of unknown origin, the tendency has been to exclude hemorrhages into the closed cavities, such as the intracranial, peritoneal, and thoracic cavities as well as the adrenal gland. If the intracranial hemorrhages are excluded, then the disease is exceedingly rare.

Le Queaux[21] found an average incidence of 1 in 2,000 births, while Holt and McIntosh[22] quote an incidence of between 1 in 100 and 1 in 1,000. The wide variation of these figures is due to the vague and varied means by which they were classified. Clifford,[23] who has done much to clarify the picture, gives the incidence to be from 1 in 118 to 1 in 133 births and includes only those showing defects in the clotting mechanism.

All are in agreement in fixing the points of bleeding, but best qualified appears to be the work of Capon[24] who states that melena alone was the most common form of hemorrhage. The usual forms in the order of their frequency are as follows:

1. Melena
2. Melena plus hematemesis
3. Melena plus epistaxis and palatal bleeding

4. Umbilical bleeding
5. Umbilical and palatal bleeding
6. Hematuria, epistaxis, and umbilical bleeding
7. Umbilical, vaginal, oral, and vulval bleeding

Almost all the fatal cases occurred in the hemorrhages of the gastrointestinal tract. His mortality for the series of sixty-one cases was 8 per cent. It must be noted that he was careful to exclude the various cases of bleeding into closed cavities. Applying this criterion of diagnosis, Clifford had no fatalities in sixty-nine cases at the Boston Lying-in Hospital. However, when he included the cases of intracranial hemorrhages plus evidence of other bleeding, his mortality was 30 per cent. No definite incidence and mortality figures can be obtained until a universal redefinition of the disease can be established. And there will be no such change unless a common etiology can be proved to exist.

At the Children's Hospital, Washington, D. C., the records present a confusing state regarding true hemorrhagic disease of newborn infants. With no definite etiological pathology, there has been no agreement concerning its classification. Based on a similarity of symptoms

TABLE I

SUMMARY OF CLINICAL SIGNS AND SYMPTOMS OF SIXTEEN CASES OF HEMORRHAGIC DISEASE OF THE NEWBORN INFANT*

SOURCE OF BLEEDING:	
Umbilical	32.0%
Melena	20.0%
Hematemesis	15.0%
Nasal and oral	13.0%
Petechia	6.0%
Hemorrhage from circumcision	6.0%
Petechia, hematemesis, and melena	8.0%
POST-MORTEM EXAMINATION, 62.0%:	
Intracranial hemorrhage, 4 cases	25.0%
Adrenal hemorrhage, 2 cases	12.5%
Peritoneal hemorrhage, 3 cases	18.5%
PROGNOSIS:	
Expired	13 cases
Recovered	3 cases
Mortality	77.0%
TREATMENT†:	
All were given intramuscular and intravenous blood.	

*From the files of the Children's Hospital, Washington, D. C. Intracranial hemorrhage excluded.

and post-mortem findings, sixteen cases of hemorrhagic disease are presented in Table I, and the average statistics are recorded. It is seen that they resemble closely the figures of Capon, stated previously. Noteworthy is the fact that the average age of onset was 3.5 days. This brings the onset of this series into the hypoprothrombinemia phase of the newborn blood. The mortality rate is high because Children's Hospital usually receives those cases that have been bleeding sufficiently long to jeopardize life. A truer representative series is to be found in a large obstetric hospital. It is during the newborn infant's stay there that the disease is encountered.

In accord, however, is the fact that fatal cases of hemorrhage do not begin with a sudden onset or gush of blood, but rather with a gradual oozing which cannot be stopped. Most of these hemorrhages occur between the second and fifth day of life. It is this characteristic picture that has called attention to the defect of bleeding and clotting in newborn infants.

In studying these fatal hemorrhages, as far back as 1913, Whipple[25] observed that prothrombin and antithrombin were in a definite equilibrium and that, when antithrombin was in excess, bleeding was to be expected. Later, he presented two cases of melena neonatorum in which the prothrombin was deficient. This was determined by the Howell method. Gelston[26] and Schloss and Commisky[27] presented cases in which they found a definite deficiency in prothrombin. One case also revealed a decrease in the fibrinogen. In 1920 Rodda,[28] reporting a series of cases, found that the bleeding time and coagulation time of the newborn infant were prolonged during the first four days of life. His work was later confirmed by Lucas.[29]

Sanford[30] at one time thought the anesthetic given the mothers was the responsible factor. Recently Sanford and Leslie,[31] studying two cases of hemorrhagic disease of the newborn infant, reported the cause to be failure of the platelets to disintegrate properly. In the normal infant they could find no effect on the bleeding and coagulation time after repeated parenteral injections of small doses of whole blood—a measure which was successfully used in one of their cases. Javert[32] came to the conclusion that there was a derangement of the prothrombin-antithrombin equilibrium which was precipitated by a dietary imbalance during the ante-natal period, thus affecting the coagulability of both the mother's and the baby's blood.

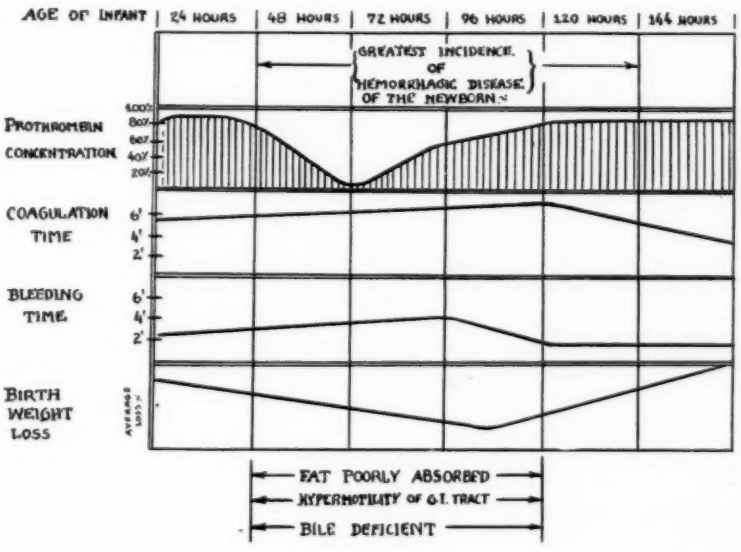
Since simplicity and accuracy have marked the approach to bleeding defects, it has been established that between the second and fifth days of neonatal life, the bleeding and coagulation times are definitely prolonged. A return to normal has been noted in each instance after ten days. In accord with this, Sanford[33] in Brenneman's *Practice of Pediatrics* states that the diagnosis of hemorrhagic disease of the newborn infant should be made only in those cases of active hemorrhage in which the bleeding and coagulation times are prolonged over ten minutes. He does not consider intracranial hemorrhage a form of this disease unless accompanied by other signs of hemorrhage. Salmonsen[34] presented a series of nineteen infants who showed signs of intracranial hemorrhage after normal period of forty-eight hours following birth. Of these, thirteen showed evidence of hemorrhage elsewhere in the body, and eleven of these were associated with a distinct prolongation of the clotting time. Seventy newborn infants with intracranial hemorrhage during the first forty-eight hours following birth were found to have normal clotting times, and none had evidence of other bleeding. Further, he studied 100 healthy newborn infants and discovered that the bleeding and coagulation times were prolonged between the second and fifth days of life. His viewpoint was that this was an expression of one of the many adjustments the newborn infant has to make. However, he compares these hemorrhages to hemophilia and demands that intracranial hemorrhage occurring forty-eight hours after birth be called hemophilia neonatorum. Treatment advised is transfusion.

PHYSIOLOGIC HYPOPROTHROMBINEMIA OF THE NEWBORN INFANT

With the apparent second to fifth day defect in the clotting mechanism established with certainty, attention was drawn to the cause of the delay. In 1939 Quick and Grossman,[35] investigating the course of prothrombin in the newborn infant, observed that at birth the prothrombin concentration was approximately normal. At the end of twenty-four hours there was a drop to very low levels, and this gradually rose until the third day, after which the prothrombin level was back to normal. These tests were performed on thirty-one normal healthy infants, and the method as developed by Quick was used. The results are given in Table II. The babies' ages ranged between 6 hours and 60 days, so that at least a representative series was studied.

TABLE II

A COMPARISON OF THE PLASMA PROTHROMBIN CONCENTRATION AND THE BLEEDING AND COAGULATION TIMES IN THE INFANT DURING THE FIRST SIX DAYS OF LIFE



These findings coincided remarkably with the delay in the clotting process during the second to fifth day of life. From these studies it was concluded that, although given prothrombin from a maternal reserve, no reserve of prothrombin was built up in the fetus, and in the first twenty-four hours of life this blood-clotting factor was distinctly reduced to hemorrhagic levels. However, it is apparent that soon this concentration begins to increase, and any delay in this recovery will give rise to a bleeding diathesis. The rise by the third day accounts for the rarity of neonatal hemorrhages. From the series studied it is logical to assume that there exists in all normal newborn infants a definite phase of "physiologic hypoprothrombinemia." This hypoprothrombinemic phase occurs from the second to the fifth day of life. Since all newborn infants are thus in jeopardy of

hemorrhage, it seems that there is a scientific basis for the ancient Mosaic law which insists that circumcision be performed not earlier than the eighth day following birth.

These findings are not in accord with the report of Brinkhous, Smith, and Warner[36] who, in 1937, determined that the prothrombin of all newborn infants averaged between 14 and 39 per cent of the normal and that it gradually rose to normal by the end of the year. Of their series only three babies were below 11 days of age. They also presented a case of hemorrhagic disease of the newborn infant in which the prothrombin concentration was below 5 per cent. The variation between our series and that of Smith has since been corrected by the modification of their prothrombin tests. Since the publication of the report, others have given similar results in their observations and it is now accepted that the prothrombin concentration decreases between the second and fifth days of life. It is interesting to note that cord blood averages about 68 per cent of the normal prothrombin values.

Grossman[37] has concluded after an investigation of fetal prothrombin that the prothrombin found in the healthy newborn baby is more unstable and deteriorates more rapidly than adult prothrombin. Also, serial dilution with normal saline causes a rapid decrease in the clotting powers of certain bloods of these normal infants. The assumption was then made that, if the cause of hemorrhagic disease of the newborn infant is to be attributed to some faulty mechanism of the prothrombin, it is possible that the marked instability of fetal prothrombin levels is in a decline (second to fifth day) in the face of an adjusting body mechanism and may be conducive to a hemorrhagic diathesis. This fact has been borne out by Smith and co-workers,[38] who shortly afterward voiced the same conclusions concerning the relative hypoprothrombinemia of the newborn infant, using the method of Quick.

FACTORS RESPONSIBLE FOR HYPOPROTHROMBINEMIA OF THE NEWBORN INFANT

As has been shown previously, there is no reserve of prothrombin in the newborn infant. Apparently this is due to K avitaminosis. There must be, however, a reason for the return of the prothrombin to normal by the end of the third day. Greaves[39] has shown that vitamin K can be synthesized by bacteria in the intestinal tract. But, since the infant intestinal tract is sterile at birth, we cannot account for the vitamin K from the bacterial synthesis. Also, similarly, the small amount of food taken during the first forty-eight hours of life can furnish little vitamin K. It is only logical to assume, then, that as soon as the infant ingests food, he infects his gastrointestinal tract with a bacterial flora destined to synthesize vitamin K for the elaboration of prothrombin. This does not take into consideration the delay of the return to normal until the fifth day, as occurs in many infants. To satisfactorily explain this phenomenon, it is necessary to recall that the liver of the newborn infant is unable to secrete sufficient bile[40] and that the capacity of these infants to absorb fats is very limited. Further, there is a hypermotility of the newborn infant's gastrointestinal tract during the first week of life. It is clear that, even though formed, vitamin K, which is fat-soluble, is not absorbed until the digestive functions approach normal on about the third or fourth day of neonatal life, thus delaying the return of normal prothrombin.

Previously it was shown that the clotting power of prothrombin decreased with dilution.[37] Hematologists will acknowledge the fact that, as the weight of the newborn infant decreases, the water content of the blood increases, so that for the first four days following birth, there is relative hydration of the blood. The weight loss of an infant begins immediately after birth and continues until the fourth or fifth day.[39] The prothrombin of plethoric blood is weak in clotting power, and this may further explain the hypoprothrombinemia of the newborn infant.

Still another mode by which we can further associate a low plasma prothrombin is the fact of the deficiency of plasma globulins in the circulating blood of the newborn infant. One of the properties of prothrombin is its unknown relationship to globulin. That there is a defect in the plasma globulins has been proved by McKhann and Edsall,[41] who believe this may be the basis of the hypoprothrombinemia of the newborn infant. Colostrum, the first maternal supply of milk, is usually denied the infant. This food is richly supplied with globulin, large amounts of which are absorbed directly into the blood stream from the intestinal tract. It is not entirely impossible that this denial of colostrum will materially affect the prothrombin content. It would prove interesting to note the possible changes of plasma prothrombin in infants fed globulin in large amounts from birth on.

METHODS TO ELIMINATE NEONATAL HYPOPROTHROMBINEMIA

Table II clearly reveals the association of the delayed bleeding and coagulation times to the neonatal hypoprothrombinemia and also the relation to the initial weight loss and digestive functions. Before assuming a definite attitude of the etiology of delayed clotting mechanism in the newborn infant, the other factors of blood clotting must be ruled out of the picture. Although Leslie and Sanford[42] believe the defect is due to a failure of the platelets to disintegrate properly until the fourth day of life, it has been shown that administration of thromboplastin solutions is of no avail.

To be sure, the rare case of the hemophilic baby may be traced to this thromboplastic inadequacy. Blood transfusion will help these cases. Only in extensive bone marrow destruction can there be a deficiency of fibrinogen sufficient to result in free bleeding. And very rarely can a congenital fibrinogen defect be found. This factor has definitely been eliminated as a cause of the clotting defect of the newborn infant.

Calcium is never the cause of hemorrhage in the newborn infant and appears to be lacking only in extreme cases of jaundice. Therapy with calcium will seldom, if ever, cause hemostasis.

Prothrombin, the remaining constituent of the blood, is the major deficiency responsible for the defective clotting mechanism. With definite proof of its inadequacy in jaundice and coincidental demonstration of its deficiency in the newborn infant, logically there should be expected a response to vitamin K therapy and the probable elimination of the hypoprothrombinemia of the newborn infant, as has been shown occurs in jaundice. In a very recent communication, Quick states that vitamin K will successfully eliminate the hypoprothrombinemia of the newborn infant and has forwarded proof for future publication. Conclusive proof has been given by the recent work of Waddell and Guerry.[43] In a series of twenty healthy new-

born babies, using ten as controls, they were able to eliminate the hypothrombinemia of the newborn infant and prevent the delay in clotting power of the blood. This was accomplished with the use of vitamin K concentrate. One cubic centimeter was given at the end of twenty-four hours, 0.5 c.c. at the end of forty-eight hours, and 0.5 c.c. at the end of seventy-two hours. They conclude that prothrombin in the newborn infant is most deficient between forty-eight and seventy-two hours following birth and returns to normal by the fifth day at the latest. This fact coincides exactly with the results obtained by Quick and Grossman.

Although the exact dose to be given these babies to prevent neonatal bleeding should be gauged by the level of the prothrombin concentration, Quick recommends that 0.5 c.c. be given orally every six hours with a medicine dropper. Bile salts should be given along with it. If this measure is started at birth, potential hemorrhages will be prevented. Other measures still in the experimental stage, which may be used to combat hypoprothrombinemia of the newborn infant, may consist of feeding him more food immediately to establish an early intestinal flora. Also, as mentioned previously, it may be wise to feed these infants large amounts of globulin from the beginning.

INTRACRANIAL HEMORRHAGE OF THE NEWBORN INFANT

It is not difficult to visualize that intracranial hemorrhage and hypoprothrombinemia of the newborn infant may be so closely associated that a definite etiology is now at hand. It is conceded that the trauma of birth may in many instances cause the appearance of small bleeding points in the intracranial cavity. However, even in normal births and in babies born of cesarean section, this has been found to exist. With an abnormal state of clotting existing, as does exist because of the hypoprothrombinemia, it is apparent that no clot will form and that the slow oozing will continue. Were the clotting powers of the blood normal, these sources of bleeding would promptly cease. This slow oozing of the bleeding points explains why the symptoms of intracranial hemorrhage usually reveal themselves on the fourth, fifth, or sixth day after birth.* By establishing a normal prothrombin concentration with the use of vitamin K by mouth in those cases that reveal delay in clotting mechanism, a new prevention for intracranial hemorrhage, excluding tentorial lacerations, may be found.

Hellman and Shettles[44] have investigated the blood picture of the premature infant and have been able to raise the extremely low prothrombin concentrations of the premature infant to within fairly normal levels by feeding vitamin K to both the mothers and infants. All their infants born of mothers who were fed vitamin K revealed a normal prothrombin content during the supposed hypoprothrombinemia phase. Because intracranial hemorrhage of the newborn infant is responsible for about 25 to 40 per cent of the fetal mortality encountered in this country, it should encourage all clinicians to give this therapy a trial and to compare the incidence of intracranial hemorrhage with a large series of vitamin K treated cases. With such a report at hand, it may be possible that a definite reclassification of hemorrhagic disease of the newborn infant may be made to include intracranial hemorrhage.

*Out of sixteen recent cases of intracranial hemorrhage at the Children's Hospital, Washington, D. C., the average age of onset was found to be 6.3 days following birth. The chief symptoms were failure to nurse and convulsions. The chief sign was cyanosis. A mortality of 67 per cent was encountered.

HYPOPROTHROMBINEMIA IN OTHER NEONATAL CONDITIONS

Not only intracranial hemorrhage, but other diseases peculiar to the newborn infant and characterized by spontaneous hemorrhages, have recently been shown to possess low prothrombin levels. Icterus gravis neonatorum, anemia neonatorum, and hydrops congenitus,[45] having a definite deficiency of prothrombin were satisfactorily treated by the administration of vitamin K. All cases in which there is a congenital obstruction to the outflow of bile will present low prothrombin concentrations and should be given vitamin K to prevent a hemorrhagic diathesis. All cases of prolonged vomiting, especially hypertrophic pyloric stenosis, will be in jeopardy of hemorrhage, and any surgery attempted during the first week of life should include a preoperative course of treatment with vitamin K. It has been found at the Children's Hospital that severe prolonged diarrhea will cause a depletion of the prothrombin content probably due to hypermotility of the intestinal tract and the faulty absorption of vitamin K from the diet. Whether or not the occasional melena without evident intestinal ulceration, which can be found in cholera infantum cases, is due to spontaneous hemorrhage high up in the intestinal tract has yet to be proved.

In older children, sprue, intestinal polyposis, chronic ulcerative colitis, intestinal fistulas, gastrocolic fistulas, and intestinal obstruction have shown delayed clotting times due to hypoprothrombinemia (Clark and associates[46]).

SUMMARY AND CONCLUSION

A new vitamin has recently taken its place among those substances destined to alleviate human suffering. This is known as vitamin K. The history of its discovery and the mode of its action are presented.

Vitamin K is absorbed in the normal intestinal tract in which there is sufficient bile and synthesizes prothrombin in the liver. A hypoprothrombinemia exists in all instances in which bile is prevented from reaching the upper intestinal tract. Given in conjunction with bile salts, vitamin K will restore a low prothrombin concentration and prevent possible hemorrhage due to this cause.

A definite hypoprothrombinemia occurs in normal infancy between the second and fifth days following birth. This accounts for the delayed bleeding and coagulation times encountered during this period. Because hemorrhagic disease of the newborn infant occurs most frequently during this period, the physiologic hypoprothrombinemia may be the responsible factor. It has been shown that administration of vitamin K to both mothers and newborn infants will prevent the usual low prothrombin concentration.

Intracranial hemorrhage of the newborn infant may be associated with the neonatal hypoprothrombinemia, and it is suggested that prophylactic administration of vitamin K will lower the incidence of these hemorrhages.

Vitamin K therapy is indicated in all surgical cases of less than one week of age. Hypoprothrombinemia associated with hemorrhagic disease of the newborn infant, intracranial hemorrhage, icterus gravis neonatorum, anemia neonatorum, and hydrops congenitus will respond to vitamin K therapy. Any disease characterized by an interference with the normal output of bile or destruction of intestinal mucosa deserves trial with vitamin K.

The suggestion is made that hemorrhagic disease of the newborn infant and its associated bleeding tendencies be classified as a vitamin-deficiency disease due to a lack of vitamin K.

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American Academy of Pediatrics

Proceedings

NINTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

CINCINNATI, NOVEMBER 16-18, 1939

Round Table Discussion of Treatment of Pneumonia in Infants and Children

Chairman: Charles Hendee Smith, B.S., M.D., New York, N. Y.
Assistants: Henry L. Barnett, B.S., M.D., St. Louis, Mo.
Glenn E. Cullen, PH.D., Cincinnati, Ohio
Secretary: L. J. Schermerhorn, M.D., Grand Rapids, Mich.

CHAIRMAN SMITH.—We can begin our discussion best by clarifying the nomenclature of the pneumonias, since this has a definite bearing upon the results of treatment. The diagnosis "pneumonia" is not sufficient.

1. *Lobar pneumonia* (Synonyms: pneumococcus, primary genuine, croupous, alveolar, localized, etc.).—This form is almost an exact equivalent in older children of the lobar pneumonia of adults. In infants the picture varies somewhat because of the different reaction to disease seen in the very young.

Lobar pneumonia is *not* a "primary" disease, but almost always follows colds or other respiratory infections. The onset of high fever and acute symptoms, however, is usually sudden. There are cough, grunting, rapid respirations, pain (pleural), prostration, and often marked nervous symptoms. A leucocytosis is the rule, often high, with a normal count occasionally. Physical signs appear on the third day, or later, or not at all. They are situated at first along the great fissure, no matter which lobe is involved. The roentgenogram shows an early, localized, homogeneous shadow in characteristic areas for each lobe, but always resting on the great fissure.

The duration, when not influenced by treatment, is two or three days to two or three weeks, usually five to eight days, depending upon the age of the patient, his resistance, and the type of pneumococcus. In infants termination is by crisis, with or without a precritical dip or postcritical rise.

Any of the pneumococcus types may be found, but mostly VI, XIV, XIX, etc., in infants, and I, V, and VII in children older than two years. This disease occurs at all ages, even in the first weeks of life. Our youngest patient who came to autopsy was 5 weeks old, but I have seen death clinically at 3 to 4 weeks of age; 28 per cent of our clinical series are in the first two years of life.

The prognosis is excellent, except in the very young or feeble infant, or in the infant with empyema or meningitis. Therefore, the disease is rare at autopsy, so rare that its existence in infancy is denied by some. Indeed, until the advent of sulfapyridine, its existence clinically was greatly underestimated, and all childhood pneumonia was referred to as bronchopneumonia. Even in 1938 Evans and Gaisford report a series of forty cases of "bronchopneumonia" attributed to the pneumococcus in children treated with sulfapyridine.

The pathology shows a fairly even inflammatory exudate into the alveoli of one or more lobes, some septal and pleural inflammation, empyema especially in Type I, and an endobronchitis, but no changes in the *walls* of the bronchi. This corresponds to the pathology of lobar pneumonia in the adult.

In the hospital, 75 per cent of our cases are this common "lobar" pneumococcus pneumonia. In private practice it is almost the only type seen.

2. In *lobular pneumonia* the exudate is into the alveoli, but distributed very irregularly in various lobules throughout the lung. At times there is confluence and involvement of whole lobes. The hilar lobules are involved more than the rest of the lung in most cases. There are no changes in the bronchial wall. There is nearly always aspirated food or vomitus in the air passages, and there may be superficial irritation or necrosis of their living mucous membranes. In a few cases no aspirated food can be demonstrated, but there is purulent matter in the air passages, apparently aspirated from the upper part of the respiratory tract. Such cases have a definite history of preceding respiratory infection.

This form is seen in feeble or premature infants, or in those with congenital defects, mostly in the early months of life. There is often a history of vomiting, choking, or of the use of gavage. The course is usually short. After a choking spell, or without it, the infant becomes sick. He may or may not have fever, cough, or physical signs. Few x-rays are taken because often the disease is not suspected. The duration is short and the prognosis bad. The autopsy usually surprises the clinician who may not have thought of pneumonia.

3. *Bronchopneumonia* is not the most common form at Bellevue Hospital, and in its pure form it is seen more rarely than lobar at the autopsy table. This disease is characterized by a specific reaction, namely, an infiltration of mononuclear cells into the walls of the bronchi. These form a collar in the submucosa, often of great thickness, and may compress the lumen of the air passage and also cause collapse of the surrounding alveoli by pressure. These areas around the bronchi contain desquamated cells, but no true exudate. Collapsed areas supplied by the bronchi are also seen, often extensive, a large part or all of the lobe. There is some endobronchitis, but no intra-alveolar exudate, no septal or pleural inflammation, and no empyema.

We see this form in young infants, from 6 months to 3 years of age. It follows a respiratory infection, an infectious disease, or comes as a terminal event at the end of a prolonged fatal illness. In its pure form we have only six autopsies, but we have many cases in which the patients recovered and in which the picture is such that this diagnosis is justified.

The temperature is irregular, not high (101° to 103°); the course is long, from two to six to eight weeks; and the defervescence is by lysis. The patient is much sicker than the height of the temperature would indicate. The respirations are rapid, often labored, but not grunting (no pleurisy), and cyanosis is frequent. The cough comes in severe bouts in which the infant coughs with every expiration until exhausted.

The classic signs are resonant or consonating râles heard at the bases of the lungs. Moist râles may also be present, but the ringing quality of the resonant râle is characteristic. In some cases bronchial breathing may be heard over all or part of a lobe (collapse?), but not in "small patches here and there." These lungs are too small for many areas of increased density to be found by examination. In the early stages the x-rays show nothing; later they show a fraying or streaking out from the hilus, but not mottling; or a thin hazy shadow over a collapsed lobe may be seen. The diagnosis must be made with a negative roentgenogram in many cases.

The bacteriology is bizarre and variable. Pneumococci may be present, but usually these are the "carrier types," rarely the common ones seen in lobar pneumonia. Streptococci are sometimes found, but not regularly enough to make it

likely that these are the true cause of all cases. There is some reason to believe this may be a virus disease. The animal experiments of McCordock, Muckenfuss, and others are suggestive of this. "Capillary bronchitis" is a diagnosis we have abandoned. A few infants do have a severe bronchitis, but we suspect that most cases are really bronchopneumonia.

4. "*Broncholobular pneumonia*" is a mixed form which shows both a peribronchopneumonic infiltration with mononuclear cells, and a patchy intra-alveolar exudate of simple inflammatory type, and pleural involvement, at times, with empyema. The proportion of these two elements varies greatly. In some there is advanced bronchopneumonia with minimal alveolar exudate, in others the lobular lesions predominate, with a very early bronchopneumonia. The clinical course of autopsied cases suggests that one group begins as a bronchopneumonia; then aspiration of infected bronchial secretion takes place and causes the lobular lesions. Another group shows aspirated matter in the air passages with extensive alveolar reactions, and apparently the patients live long enough to develop early bronchopneumonia. Other cases start like a lobar pneumonia and are difficult to differentiate at first, although we make the diagnosis correctly in many cases as the disease progresses. This form is also seen after infectious diseases.

The course is variable. Some cases are sick only a short time; others are prolonged, with high irregular fever. The signs vary with the extent of consolidation and the amount of bronchial reaction. The x-ray often shows mottled irregular shadows suggestive of tuberculosis, or which, when localized, are less dense and less classically placed than in lobar pneumonia. Pneumococci or streptococci may be found, but not in all cases. When staphylococci are present, there has usually been a fatal result in our experience and frequently empyema from the rupture of a subpleural abscess.

We suggest that broncholobular pneumonia may be a mixed infection with virus and pyogens. We have coined this term because each of its elements is seen as a pure form. It is much more fatal than pure bronchopneumonia. We have fifty-four such autopsies, all in children under 2 years of age.

5. "*Subacute pneumonia*" is a term we use to describe a form seen in older children. We have no autopsies, since it has invariably ended in recovery. It falls into three rough groups.

The first resembles an acute pneumonia at the onset. Following a cold, the temperature suddenly rises; there is cough with profuse expectoration, some chest pain, and moderate prostration. The fever is irregular, not high, and runs a course of a few days to three to four weeks, ending by lysis. There is a marked leucocytosis which often persists after the fever has ceased. The signs are those of a basal bronchitis with resonant râles, and sometimes, signs of consolidation. The x-ray shows mottled or streaked shadows at the bases, which may persist for weeks after defervescence.

The second group has much the same story, signs, and shadows, but somewhat less fever. It is often mistaken at first for a pneumonitis complicating bronchiectasis. In both of these the x-ray and bronchogram become normal after several weeks.

The third group resembles so-called bronchosinusitis, but there is a real pneumonia as shown by the signs and shadows. There is no residual lesion in the bronchogram and x-ray.

This "subacute" pneumonia is a common disease, and we have records of several hundred cases. It is probably what Riesman has described as a "lobar form of bronchopneumonia," but we feel that no pathologic name should be attached to it so long as there is no autopsy proof of its nature. It may be a variety of broncholobular pneumonia in the older child, with a good prognosis. The x-rays are suggestively like those of some of the fatal cases in infants. The bacteriology is inconstant, and perhaps this too is a mixed infection with virus and pyogen.

Other forms of pneumonia need only be mentioned—septic pneumonia in general sepsis, congenital pneumonia due to aspiration of infected liquor amnii, the acute interstitial pneumonia of infants in which there is a severe lymphangitis of the septa only and no parenchymal involvements. Streptococci have seemed to be the cause of the last mentioned.

Specific Treatment

Glenn E. Cullen, Ph.D., Cincinnati

Our experience with chemotherapy in the treatment of the pneumonias in children has been limited to sulfapyridine, with the exception of four children who received hydroxyethyl-apo-cupreine. In discussing the value of the use of sulfapyridine in children, I think it worth while to emphasize the plan of our study, because we feel that far too many of the studies on sulfapyridine have been inadequately controlled. For comparison with other workers, geographic and economic variants are always present. Even in our community there are great seasonal fluctuations in severity of the disease. Because of the low case fatality in pneumonia in children, we felt it necessary to use some other criterion and, therefore, selected three; first, a significant fall in temperature; second, the duration of the disease before the first evidence of maintained clinical improvement; and third, the duration before clinical recovery. Since the last two criteria are subjective and depend upon the clinical judgment of the observer, we felt it important, so far as possible, that these criteria be ascertained by the same persons. The allocation of patients to the group to be treated with sulfapyridine and to the control group is not simple, especially for children. We decided that the time-honored method of assigning alternate cases to the control and study groups was not satisfactory because of the variations in such factors as age, state of nutrition, duration of the disease, severity, etc. Therefore, we had recourse to what may be called the selective allocation of patients, in which a chart was kept of cases assigned to both groups and a careful attempt made to keep the two groups in balance in regard to all these factors. This idea is not original

TABLE I

ANALYSIS OF SEVENTY CASES OF PNEUMONIA

	CONTROL GROUP (TOTAL, 35)	SULFAPYRIDINE GROUP (TOTAL, 35)
Age		
0–11 mo.	9	8
12–23 mo.	9	8
2– 4 yr.	10	11
5 yr. and over	7	8
Severity		
Mild	4	1
Moderate	16	15
Severe	13	17
Very severe	2	2
Estimated duration of pneumonia on admission		
1 day	3	1
2 days	14	12
3 days	9	11
4 days	3	7
5 days	4	2
6 days	2	1
7 days and over	0	1
Average	2.9	3.1
Type of pneumonia		
Croupous pneumonia	22	20
Bronchopneumonia	11	13
Unclassified	2	2

with us; it has been discussed most adequately by Mainland, but it is a principle which certainly should be considered in all clinical investigations. By rigid adherence to this principle of selective allocation of patients, we feel that, for the first seventy patients of our study, the control and study groups had satisfactory similarity of the variables which have been mentioned. Table I shows just how satisfactorily this principle works out.

Subsequent events during the winter and spring of 1939 proved that this was a most fortunate decision, for the impression of the entire clinical group was that the pneumonias of this year in Cincinnati differed definitely in severity from those of previous years.

The analysis of our results was made much easier and more accurate by the use of a special chart designed for the purpose. In the analysis the data of four patients were rejected for adequate reasons, and it happened that thirty-three of the patients fell into the control group and thirty-three into the study group. The results are shown in Table II.

TABLE II

CLINICAL RESULTS IN SIXTY-SIX CASES OF PNEUMONIA

	CONTROL GROUP, 33	SULFAPYRIDINE GROUP, 33	DIFFERENCE IN DAYS	P
Mean day of pneumonia at				
Clinical improvement	7.0	4.0	3.0	<0.01
Significant fall in temperature	8.1	4.7	3.4	<0.01
Clinical recovery	11.2	7.5	3.7	<0.01
Mean day of treatment at				
Clinical improvement	4.4	1.9	2.5	<0.01
Significant fall in temperature	5.3	1.9	3.4	<0.01
Clinical recovery	8.9	4.7	4.2	<0.01

It is evident that the duration of the illness, from whichever criterion was used, was reduced from 2½ to 4 days by the use of sulfapyridine.

A rigorous analysis of these differences by the type of statistical analysis which we deemed most suitable for studying a small group of persons indicates that this difference in days is statistically significant.

Because of the change in personnel in the wards of our hospitals, we are sure that the control groups, subsequent to the first seventy cases, do not furnish anywhere nearly as adequate a control as the first thirty-five cases in the control group. What actually happened was that a disproportionate number of infants and children with very severe pneumonia were put in the group to be treated with sulfapyridine. One must rely on the assumption that the character of the disease in the late months of the winter was not essentially different from that of the first part in making an analysis of the results obtained with sulfapyridine during these months. Because of *our* difficulties in obtaining satisfactory control conditions, we feel that we cannot overemphasize the importance of much more rigorous attention to all the factors that go into making a satisfactory control group in any study involving children, not to mention adults.

In spite of the fact that the drug group was somewhat unbalanced against the drug, an analysis of the three criteria—average treatment at which a significant fall in temperature occurred, average day of maintained clinical improvement, and average day of recovery—came out practically the same as for the group previously reported.

We have summarized all our cases in Chart 1 upon which is represented the distribution by patients for the day on which there was significant fall in temperature. There can be no question of the effect of the drug in reducing temperature.

In the pneumonias in children the incidence of complications is a problem of great importance. An attempt to compare values for this in the two groups suggested that complications appear less often in the sulfapyridine group than in the control group, but the number of cases of complications is rather few for statistical analysis. However, in the entire series the incidence of empyema was six times as great in the control group as in the group receiving sulfapyridine, i.e., six in eighty control patients as compared with one in eighty-four patients on the drug.

Although the statistical analysis of the results of such a study is probably the best way in which it can be evaluated, it is necessary to emphasize that results in individual cases must be considered; the results of our study differ from most of those reported in the literature, especially in regard to children, in one very essential difference, in that, although, as shown, there is no question that the group receiving sulfapyridine has the disease shortened as compared with the control group, not every patient with pneumonia responds to treatment. We have had six cases which did not show any response to the drug, even though we were sure that an adequate level of sulfapyridine was maintained in the blood, and an additional six patients in the sulfapyridine group had relapses. We are certain that every case of pneumonia in children will not respond to sulfapyridine therapy.

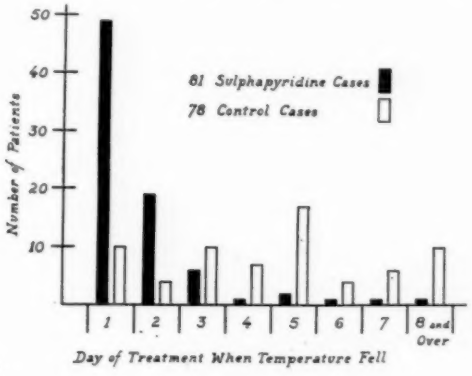

Chart 1.

In discussing the toxic effects of the drug, our experience has been somewhat contrary to that reported by others. In the first place, we have not had anywhere near the amount of vomiting and nausea that we expected. In none of the first thirty-five cases discussed above was the vomiting so severe that it was necessary to discontinue the drug, and in all cases the vomiting ceased shortly, although the drug administration was continued. In two or three later cases vomiting was sufficient to warrant discontinuing the drug. Curiously enough, we have found no reference elsewhere to the amount of vomiting in control groups, and, of course, everyone here realizes that a young child with any type of respiratory infection is liable to vomit; thus, in our first seventy cases we had eleven patients in the control group who vomited, compared with fifteen who were receiving sulfapyridine. We had eleven patients in the control group showing irritability, as compared with sixteen in the sulfapyridine group. In only one of our patients was there sufficient cyanosis to cause concern, although it is noteworthy that sixteen children manifested cyanosis on admission, and it is of interest that the cyanosis in patients receiving sulfapyridine was much less than has been observed in our hospitals for patients receiving equivalent amounts of sulfanilamide. Although there had been no deaths in either the control or sulfapyridine groups among the first seventy patients,

there were two deaths late in the spring. One was a 4-month-old infant; the other was 14 months old. They were originally in the control group but failed to respond to both sulfapyridine and specific sera.

Although, logically, the question of dosage should be taken up in the beginning of such a report as this, I have left it to treat more extensively here. We have come to the conclusion that sulfapyridine and sulfanilamide belong to the group of drugs which should not be administered unless one has the facilities for following blood levels. We feel this is desirable both for the evaluation of adequate dosage and for the discussion of toxic effect. Since there has been considerable difference of opinion as to the proper way to start the treatment with sulfapyridine, we have spent considerable time in analyzing the blood levels resulting from dosage based upon definite amounts per pound per day. Tables III and IV show the results, as far as blood levels are concerned, of the dosage employed in this system.

TABLE III

DISTRIBUTION OF PATIENTS ON BASIS OF AVERAGE BLOOD LEVEL OF FREE SULFAPYRIDINE

BLOOD CONCENTRATION (MG. PER 100 C.C.)	NO. OF PATIENTS RECEIVING 1 GR. PER LB.	NO. OF PATIENTS RECEIVING 1½ GR. PER LB.
1.1– 1.9	9	0
2.0– 3.9	27	9
4.0– 5.9	20	16
6.0– 7.9	8	16
8.0– 9.9	2	8
10.0–11.9	1	6
12.0–13.9	0	2
14.0–15.9	0	2

TABLE IV

DISTRIBUTION OF PATIENTS ACCORDING TO THE VARIATIONS OF FREE SULFAPYRIDINE LEVELS IN BLOOD IN PATIENTS ON REPEATED DETERMINATIONS

DIFFERENCE BETWEEN HIGH AND LOW BLOOD LEVELS (MG. PER 100 C.C.)	NO. OF PATIENTS RECEIVING 1 GR. PER LB.	NO. OF PATIENTS RECEIVING 1½ GR. PER LB.
2	7	2
4	17	16
6	7	13
8	1	13
10	1	3
12	1	2
14	0	1
16	0	0
18	0	2

I will not trouble you with the data in regard to the selection of these patients. It shall suffice to say that they cover varying age groups so that we should have a good cross section of the type of cases with which we have to deal. Chart 2 gives the distribution of values of sulfapyridine in blood compared with age. As you can see, the average values for all the determinations for each age group come out surprisingly close. I would not have you think that the level obtained for each patient is anywhere nearly so constant, and we have, therefore, summarized the distribution by patients, as shown in the accompanying chart. These data are sufficient to show that the system of giving dosage on the basis of pounds per day results in a satisfactory level of sulfapyridine.

It is to be noted that the greater part of the levels for each drug dosage, i.e., 1 and 1½ gr. per pound per day, fall into two drug levels. We obtained thera-

peutic results with a level as low as 2 mg. per 100 c.c. We later raised our dosage to the 1½ gr. level to eliminate the few patients who might not attain at least the 2 mg. level and to study the effect of the higher dosage. We have no indication that it is any better than the 1 gr. dosage and have recommended the attainment of about 4 mg. level per 100 c.c. as the most logical level so far as present knowledge goes.

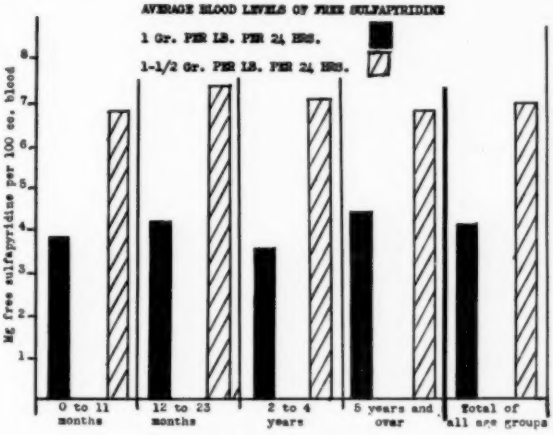
AVERAGE BLOOD LEVELS OF FREE SULFAPYRIDINE
1 Gr. PER LB. PER 24 HRS.
1-1/2 Gr. PER LB. PER 24 HRS.
Mg free sulfapyridine per 100 cc. blood
0 to 11 months
12 to 23 months
2 to 4 years
5 years and over
Total of all age groups

Chart 2.

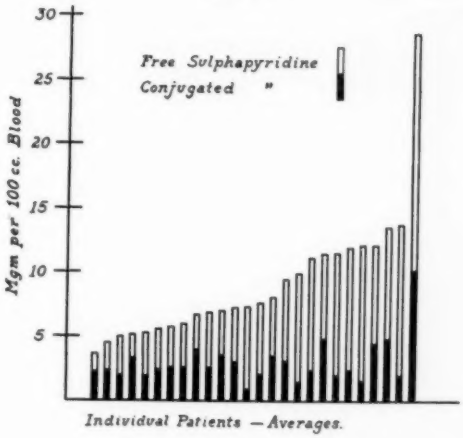

Chart 3.

Although not immediately concerned with the dosage, I think it might be worth while to show you Chart 3 which gives the results which we obtained in regard to the amount of conjugated sulfapyridine in free blood. Most of the reports dealing with the conjugation of sulfapyridine have reported them in percentage of the drug conjugated. This may be somewhat misleading, since we are really interested in the level of free drug and probably should be in the level of the conjugated drug. The chart has interested us a great deal, because it becomes quite apparent that until we reach fairly high levels of total sulfapyridine in the blood, the

amount conjugated tends to remain at constant levels less than 4 mg. per 100 c.c. The value for the one extremely high one at the right represents only one case. The rest of the values represent average of several determinations in single persons. There are various possible physiologic reasons for this apparent constancy of conjugated sulfapyridine, but a great deal of work needs to be done before a conclusive answer can be made.

In conclusion I should like to emphasize that we feel certain that this drug does reduce the duration of the disease and probably the amount of complications and is, therefore, a most desirable agent for the treatment of selective cases of pneumonia. We are not certain that it should be used *routinely* and indiscriminately in the pneumonia of children over 2 years of age. Many questions remain unanswered. So far we do not have final evidence as to the relationship between the amount of drug existing in the blood and the therapeutic effect. There is also lacking information as to the subsequent effect on individual patients from large doses of sulfapyridine. Since it is becoming increasingly evident that the action of this group of drugs depends on some interference with the enzymatic system in the body, we must be on the lookout to evaluate deleterious secondary effects, such as damage to the liver, kidneys, and other tissue. .

Lobar Pneumonia: Specific Treatment by Chemotherapy

Henry L. Barnett, M.D., St. Louis

Our results at St. Louis Children's Hospital in the treatment of lobar pneumonia in infants and children with sulfapyridine have been quite comparable to those cases mentioned and to the many reported in the literature. An analysis of the first hundred treated cases of this type of pneumonia reveals some interesting facts. Thirty-one per cent of these patients were less than 2 years of age. In 78 per cent of the cases a critical temperature fall occurred within twenty-four hours, and in 98 per cent, within forty-eight hours after the drug administration was begun. This becomes of even more significance when it is observed, as shown in Chart 1,

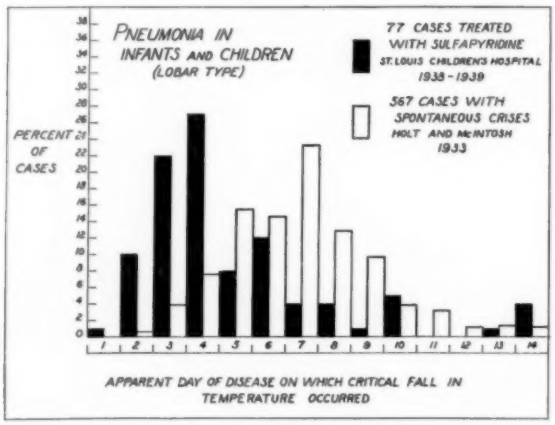
PNEUMONIA IN INFANTS AND CHILDREN (LOBAR TYPE)
77 CASES TREATED WITH SULFAPYRIDINE ST. LOUIS CHILDREN'S HOSPITAL 1938-1939
567 CASES WITH SPONTANEOUS CRISES HOLT AND McINTOSH 1933
PERCENT OF CASES
APPARENT DAY OF DISEASE ON WHICH CRITICAL FALL IN TEMPERATURE OCCURRED

Chart 1.

that 60 per cent of the cases had the critical fall in temperature during what was apparently the first four days of the disease. It would appear from this that, regardless of the day of the disease on which the drug therapy is started, a fall of the temperature to normal can be fully expected within forty-eight hours. In general, it has been our impression that the fall in temperature is followed by as

rapid clinical improvement as we are accustomed to see in untreated cases. A secondary rise in temperature did occur in 10 per cent of the treated cases. This was not an immediate upswing following the initial fall, but usually occurred on the second or third day following, and in most cases was only a temporary rise to temperatures slightly over 38° C. It was not accompanied by any recurrence of symptoms, nor did it have the characteristics of the usual drug fever. No variation in the response of different types of pneumococci to sulfapyridine could be demonstrated in our series. Ten per cent of the cases had positive blood cultures, which were distributed between Types I, VII, and XIV. There were no deaths in the bacteriemic cases. There were two deaths in the 100 cases, one of which occurred less than twelve hours after treatment was begun, so that excluding this case, the mortality was 1 per cent, which in a group with 31 per cent of the patients below 2 years of age must be considered significant. That sulfapyridine is an effective therapeutic agent in pneumococcus lobar pneumonia, however, is now fairly well accepted generally, despite the fact that it was introduced only eighteen months ago; now, rather than deciding whether or not it should be used, it becomes of more importance to decide how it should be used, and particularly important to know the dangers attendant to its use.

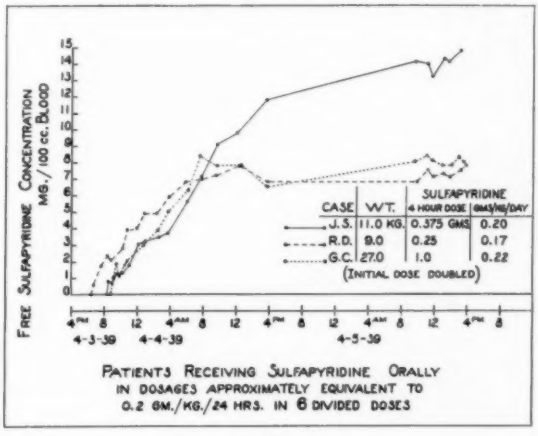

Chart 2.

Shortening the period of treatment of pneumococcus lobar pneumonia with sulfapyridine in order to avoid some of the toxic effects is now being advocated by some, which is a policy to which we cannot wholly ascribe, since, as later discussed, the more serious toxic effects do not occur during the ordinary periods of treatment with ordinary dosages unless there is a marked idiosyncrasy, in which case the drug would be stopped anyway. The average duration of treatment in our cases was five days for the infants and four days for the children. Neither the minimal effective nor the optimum blood levels of the drug in the treatment of this disease are known with certainty, but from a comparison with our experiences with sulfanilamide, our preference would be for full dosage administered as early as possible with as rapid decrease in the dosage as the clinical course permits. This has led us to adopt the following plan of oral sulfapyridine therapy in pneumococcus lobar pneumonia: The beginning dosage is calculated on the basis of 2.0 Gm. per kilogram body weight per twenty-four hours in six divided doses, the initial dose being double the divided dose. As soon as the temperature has become normal, this dosage is reduced by one-half, which is continued for from three to four days,

provided the temperature remains within normal limits and there are no direct complications.

Despite the observed irregularity of the absorption of sulfapyridine when given by mouth and the discussions concerning the subsequent therapeutic difficulties with oral administration of the drug, it is our feeling that, in the treatment of the ordinary case of pneumococcus lobar pneumonia, effective blood levels will in most cases be obtained and maintained if adequate dosages of the drug are given. As can be seen from Chart 2, the final blood level of the drug at which equilibrium is established varies considerably in different patients receiving equivalent dosages, but until more is known of optimal blood concentrations, a more closely controlled level does not seem necessary.

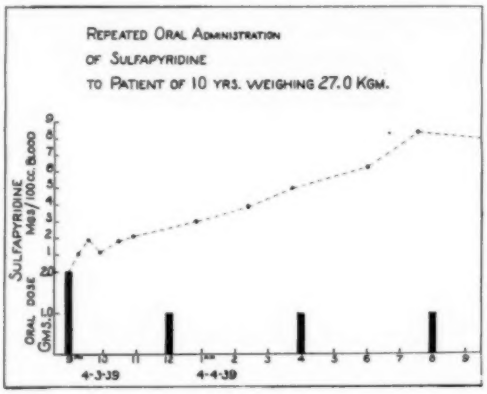

Chart 3.

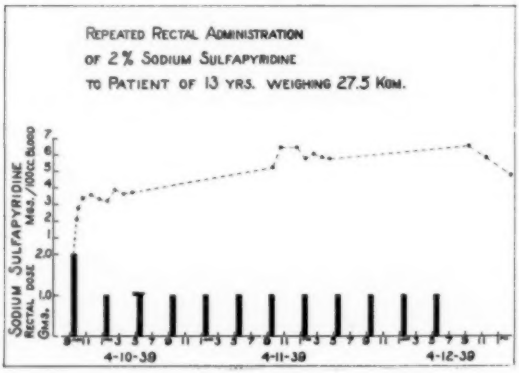

Chart 4.

Although severe nausea and vomiting do not often seriously interfere with adequate oral administration of sulfapyridine in infants and children, in the occasional pneumonia patient, particularly in the older age group, and in many of the more severe pneumococcic infections, particularly meningitis and peritonitis, the oral administration becomes quite difficult, if not impossible. In such cases, it is far less disturbing to the patient if advantage is taken of the soluble sodium salt

of sulfapyridine for administering the drug. This compound dissolves in water to the extent of 63 Gm. in 100 c.c. at 25° C. It cannot, however, be given subcutaneously because the pH of a 1 per cent solution is 10.4, and this high alkalinity would cause marked tissue reaction. We have, however, administered this form of the drug both rectally and intravenously. Charts 3, 4, and 5 compare the rates of absorption of sulfapyridine orally with sodium sulfapyridine rectally in terms of the blood concentrations, and it can be seen that the latter is of comparable promptness and completeness. For the rectal administration of the sodium salt we have employed a 2 per cent solution, of which we have given 4 c.c. per kilogram of body weight as a retention enema for the initial dose, and followed this by repeated administration of 2.0 c.c. per kilogram of body weight every four hours. Using a 5 per cent solution of the sodium salt intravenously, we have given dosages of 1 c.c. per kilogram of body weight. Charts 6 and 7 show the blood concentrations following single and repeated intravenous injections of the sodium salt. The rapid diffusion of the drug from the blood stream into the other body fluids, as shown by the quick fall of the very high concentration observed immediately after the injection, would seem to indicate that fairly uniform concentrations may be obtained by this route. The prolonged period during which the concentration remains fairly constant after the initial rise following a single intravenous injection is interesting and not entirely explainable. Because of this, however, it may be possible to maintain adequate blood concentrations with the repeated injections spaced at intervals of as long as twelve hours. Because of the nausea and vomiting experienced by some patients receiving sodium sulfapyridine by either of these routes, it seems evident that these toxic effects of the drugs are at least in part due to central irritation.

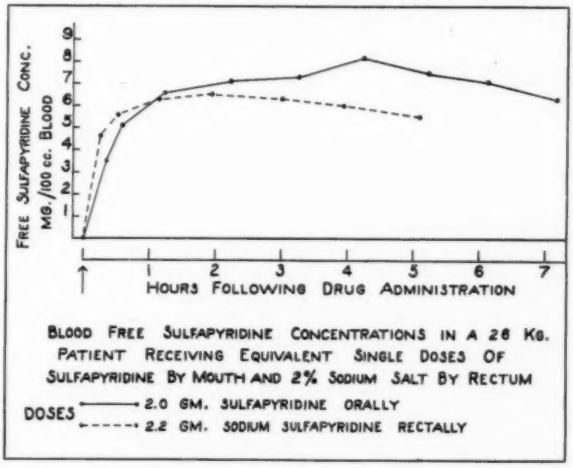

Chart 5.

In general the toxic effects of sulfapyridine are similar to those of sulfanilamide, but there are several important differences. Nausea and vomiting accompanying sulfapyridine administration have been mentioned. Besides resorting to the use of the soluble sodium salt, various ways of presenting the drug for oral administration may be tried to overcome these effects. Mixing the drug with water or fruit juices is sometimes helpful, and we have seen some children who tolerate it better when the powdered form is mixed with a small amount of applesauce or jelly and

given on a cracker. The use of alkali, nicotinic acid, and an atmosphere with high oxygen concentration has also been recommended. Disturbances in the red and white blood cells similar to those observed during sulfanilamide therapy occur with sulfapyridine, and the importance of doing frequent blood counts is equally great. Drug fever and rashes similarly occur. With sulfapyridine, the occurrence of urinary concretions, composed mostly of acetylsulfapyridine, has been described in experimental animals, and many cases of hematuria occurring in patients during the course of sulfapyridine therapy have been reported, which, in certain instances, has been associated with evidences of nitrogen retention, decreased renal function, and even anuria. We have observed a transient hematuria in about 1 per cent of our cases. Adequate fluid intake during the course of sulfapyridine therapy should lower the incidence of this toxic effect, and if it does occur, the drug should be stopped and fluids should be urged. We have been particularly interested in two of the toxic effects of sulfanilamide which concern the cyanosis and the change in

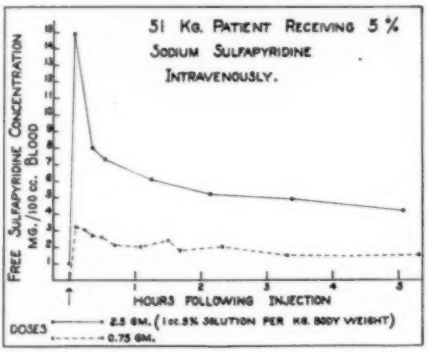
51 Kg. Patient Receiving 5 % Sodium Sulfapyridine Intravenously.
Free Sulfapyridine Concentration Mg./100 cc. Blood
Hours following injection
Doses
2.5 Gm. (1 cc. 5% solution per Kg. body weight)
0.75 Gm.

Chart 6.

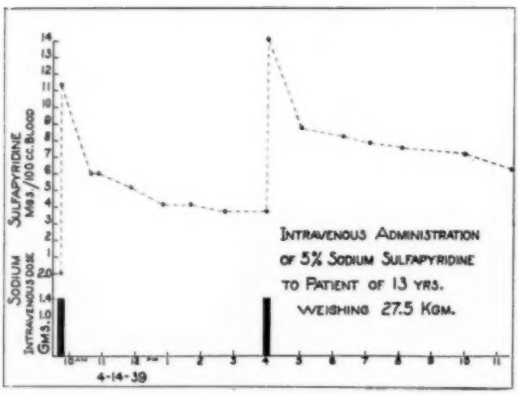
Sodium Sulfapyridine Mgs./100 cc. Blood
Intravenous dose Gms.
Intravenous Administration of 5% Sodium Sulfapyridine to Patient of 13 yrs. weighing 27.5 Kgm.
4-14-39

Chart 7.

the acid base balance. The former of these is also of importance in sulfapyridine therapy. Clinically, it would appear that cyanosis is a less constant early effect of sulfapyridine than of sulfanilamide therapy, and it seems to act somewhat differently, in that we have often seen a very intense degree of cyanosis develop very suddenly after three to four days of sulfapyridine therapy, in contrast to the more

gradual development which we are accustomed to see with sulfanilamide. It is now agreed by most investigators that the cyanosis accompanying the use of these drugs is, in most cases, due to the accumulation of methemoglobin and is thereby associated with a reduction in the oxygen-carrying capacity of the blood. This may attain values as high as 40 per cent of the total pigment; particularly in pneumonia, where oxygen want is present from another cause and where it is very important to determine whether an existing cyanosis is on the basis of poor aeration or merely due to excessive methemoglobin accumulation, it is very desirable to reconvert the methemoglobin to hemoglobin quickly, and yet to continue the drug rather than wait for a spontaneous reconversion to occur. This can be done quite simply by the use of methylene blue, which can be given either intravenously or by mouth. The dose intravenously is from 1 to 2 mg. per kilogram of body weight given in the form of a 1 per cent solution. For the oral administration, 1 or 2 gr. of methylene blue can be given with each dose of sulfapyridine.

The efficacy of sulfapyridine in pneumonias of types other than lobar (pneumococcus) is obviously less striking and more difficult to evaluate. We are particularly concerned about the "broncholobular" type of pneumonia, with a more or less diffuse, but patchy, type of intra-alveolar exudate, and in which pneumococci are often recovered. Even if the pneumococci are not the sole etiological agents in such cases, they seem sufficiently responsible for some of the toxicity to warrant treatment with serum when available, as was shown by Dr. Nemir. Similarly, sulfapyridine appears definitely to act favorably in such cases, and its value in this disease characterized by a very high mortality rate may be of even more importance than in the lobar type of pneumonia. The evident effectiveness of sulfapyridine against the streptococcus and the apparent effectiveness against the staphylococcus add to the conviction that sulfapyridine should be used in these cases.

There is little reason to believe that sulfapyridine will exert any beneficial effect in the true form of bronchopneumonia, or in the true acute or chronic forms of lobular (aspiration) pneumonia. It is our feeling, however, that, by the time these are seen in the hospital, they may be, and are so commonly, associated with perhaps secondary bacterial (pneumococci, streptococci, staphylococci) infection which materially contributes to the general toxicity, that a trial period with sulfapyridine seems warranted.

Treatment of Pneumonia by Oxygen

The main, and probably only, indication for oxygen therapy in the treatment of pneumonia is the presence of cyanosis due to poor aeration of the blood. (It must be remembered that the cyanosis due to methemoglobin accumulation which accompanies sulfapyridine therapy does not respond to an increased oxygen content of the inspired air.) In these cases oxygen therapy, if successfully given, may relieve many of the distressing signs and symptoms, and may, in some cases, be life saving. In general, an oxygen concentration of 40 per cent seems most desirable, and this can be obtained satisfactorily, at least in smaller children, only by the use of the oxygen tent or the Burgess box.

At St. Louis Children's Hospital, for the past two years we have used the simple bedside analyzer devised by Dr. Robert Huntington for determining the approximate oxygen concentration in oxygen tents. Since oxygen treatment may not be successful in anoxemia for a number of reasons other than errors of technique, as has been pointed out by Dr. Blankenhorn, the technique of oxygen administration must be carefully ordered, and since, at times, it may be of great importance to determine if adequate oxygen concentrations are being obtained, the method mentioned for this may merit a brief description.

As in other bedside analyzers, oxygen is absorbed on moist copper screening with which it comes in contact as the gas sample displaces an ammonia-ammonium salt

solution from the absorption chamber. Withdrawal of the sample from the chamber brings the solution back to dissolve the oxide and prepares the copper for the next analysis. The apparatus appears to have certain advantages over other bedside analyzers based upon the readily rinsed connections; the use of the syringe for all measurements, which obviates the necessity of a second scale; the ease with which solutions or even copper may be renewed; the compactness and sturdiness of the mounting; and the simple construction which requires neither cement nor glass blowing.

Discussion of Sulfapyridine

Charles Hendee Smith, M.D., New York

The experience at Bellevue Hospital with sulfapyridine in the period from January to July of this year corresponds with that in other cities. We abandoned the thought of controls, or a statistical approach, as soon as the miraculous and constant results were obtained in the early cases. Past experience supplies enough controls as to the probable duration and mortality of pneumonia. While pneumococcus pneumonia in older children is rarely fatal, it may be so when complicated by empyema or meningitis. Occasionally, protracted pneumonia alone may kill an older child, and there is an appreciable death rate in infants. Therefore, we feel that all cases should be given the advantage of the drug. Carey and Cooley,* of Detroit, group all "pneumonias" together. They report 10 per cent without x-ray shadows (perhaps bronchopneumonias, although they may not have ruled out concealed shadows, by lateral and eccentric films). They also report a death rate of 4.3 per cent in all infants, and of 3.6 per cent even in selected cases. No other observers have seen this in lobar pneumonia at any age after the use of sulfapyridine; therefore, perhaps these deaths represent fatal bronchopneumonias. Wilson and associates† in their series included lobar pneumonia and bronchopneumonia, but reported no deaths. In our experience sulfapyridine has no apparent effect on bronchopneumonias. We have had only eleven cases this year, with four deaths, which is about what we have seen in past years. In pneumococcus pneumonia we have had no deaths at any age (except one from pyopneumothorax). Our results are to be published in the J. A. M. A. (November 18, 1939), q.v.

Briefly, in sixty-nine of seventy-nine lobar pneumonias a crisis occurred in twenty-four hours. In three more the temperature was normal in forty-eight hours. Five cases had a crisis in one day, with secondary rises several days later. In four patients the drug was given again with prompt defervescence, and in one who received no more drug it was equally prompt. I doubt if these were true relapses. Certainly everyone sees these one-day shoots in hospital cases, due to insignificant causes.

Our dosage has been 1½ gr. per pound the first day, and usually half that amount thereafter. We have not doubled the first dose in most cases, since there is no great hurry, and the larger the dose, the more likely it is to be vomited. This is an easy plan and safer than the dose by age recommended in early papers. We believe that the older children may need even less, although in infants, and especially in Type XIV, this dosage seems necessary. The exact optimum blood level remains to be determined. I suspect it is not very high. The drug is given with cereal, applesauce, orange juice, or in part of the formula, but not on an empty stomach. We decided early to see how little we could give, and shortened the time to from one to three days. The average time was about two and one-half days. Others have had equally good results with short-time administration. Baker and Naumer‡ treated fifty-three cases for an average of two and one-half days. Others

*J. PEDIAT. 15: 613, 1939.
†J. A. M. A. 112: 1435, 1939.
‡Brooklyn Hosp. J. 1: 217, 1939.

have precipitated a crisis with one or two large doses. In our series the total amount given to infants averaged about 40 gr., and to older children, about 85 gr. The maximum given to any child was 200 gr. in one of the earliest cases in a large child. Allison* reports an average dose of 7 Gm. (105 gr.) for children.

We have seen no cyanosis, no apparent liver or kidney damage, nor any effect on the blood count. Some of the babies who developed a high blood level became very restless and excited. I question the desirability of any method for routine use which gives blood levels of 14 to 15 mg. per cent, as is seen when the sodium salt is given intravenously. Perhaps this method should be reserved for cases which can retain the drug no other way.

There have been several fatal cases in New York on the long continued administration of sulfapyridine. There is no reason evident at this time why it should be given more than one or two days after defervescence. This drug is a two-edged sword and has many toxic possibilities.

We have had one empyema present on admission and one fatal pyopneumothorax. No empyema has developed after treatment.

DISCUSSION

Thursday A.M., Nov. 16, 1939

DR. W. CLIFFORD VANCE, RICHMOND, IND.—Does an empyema present at the time sulfapyridine administration has begun become sterile with continued drug administration without drainage?

CHAIRMAN SMITH.—We had one case and did not have to drain it.

DR. BARNETT.—We had eight cases, five of which had to be drained.

DR. D. J. PACKMAN, CHICAGO.—The mortality rate and incidence of complications vary with the organisms found, and in pneumococcus pneumonia with that specific type found. Would it not be advisable to separate the group according to organisms and types, as well as age distribution, for further study?

CHAIRMAN SMITH.—All pneumococcus lobar pneumonias respond to sulfapyridine, and it is not necessary to separate the group according to organisms and types as well as age distribution.

DR. JOSEPH E. MCCLELLAN, CLEVELAND.—What effect does sulfapyridine have on cases with positive blood cultures?

DR. CULLEN.—We had two patients with positive blood cultures who died.

DR. BARNETT.—We had seven patients with positive blood cultures, and none of them died.

CHAIRMAN SMITH.—We had one patient with positive blood culture and he lived.

DR. JAMES F. CLANCY, HAMMOND, IND.—Some clinics are using serum routinely if the temperature does not drop in forty-eight hours with sulfapyridine. What do you think of this treatment?

CHAIRMAN SMITH.—All pneumococcus lobar pneumonias respond to sulfapyridine, and serum is not necessary in true lobar pneumonias.

DR. LEWIS.—How do you prevent pneumonia?

CHAIRMAN SMITH.—Have children wear sufficient clothing when they go outdoors, and when they develop colds put them to bed until they are well.

DR. TOM J. MCELHENNEY, AUSTIN, TEXAS.—How do you take care of coughs in pneumonias?

CHAIRMAN SMITH.—By codeine.

DR. CLANCY.—Do you use transfusions in pneumonias?

*New York State J. Med. 39: 1558, 1939.

CHAIRMAN SMITH.—In toxic lobar pneumonias and bronchopneumonias, yes.

DR. WILLIAM W. McKIBBEN, MIAMI, FLA.—Do you use diathermy treatments in pneumonia?

CHAIRMAN SMITH.—I have had no experience with diathermy.

DR. NOEL G. SHAW, EVANSTON, ILL.—Why do you feel that oxygen is not indicated in pneumonias unless there is cyanosis?

CHAIRMAN SMITH.—I see no reason for indiscriminate use of oxygen. Cyanosis is the indication for its use.

DR. DAVID J. LEVY, DETROIT.—How do you recognize intercurrent sulfapyridine fever in the already febrile child?

DR. BARNETT.—The sulfapyridine fever usually comes on after the continued use of sulfapyridine for several days, and one is usually able to distinguish it from the fever the child has been having.

Friday A.M., Nov. 17, 1939

DR. JOSEPH W. EPSTEIN, CLEVELAND.—How do the mortality rates compare in the two series?

CHAIRMAN SMITH.—The death rate from lobar pneumonia in older children is, of course, very low. Type XIV particularly does cause deaths in infants. In bronchopneumonia death rates are higher, and, for this reason, mortality figures based on a series of cases of undifferentiated pneumonias mean nothing.

DR. ROY N. ANDREWS, MANKATO, MINN.—Will Dr. Barnett please clarify the matter of dosage (by the intravenous method).

DR. BARNETT.—We give 1 c.c. of 5 per cent solution of sodium sulfapyridine per kilogram body weight. This dosage could be repeated at twelve-hour intervals, but usually one dose is sufficient.

DR. JOHN E. BROWN, JR., COLUMBUS.—I would like to hear more details regarding the intravenous and rectal administration of sodium sulfapyridine.

DR. BARNETT.—Both solutions are made up in sterile water. We are not certain what an isotonic solution of sodium sulfapyridine is. The solution for intravenous injection is boiled for three minutes. We precede the rectal administration by a cleansing enema and then give 2 c.c. of 2 per cent solution per kilogram every four hours. Intravenously, 1 c.c. of 5 per cent solution per kilogram is given once.

DR. ROGER L. J. KENNEDY, ROCHESTER, MINN.—What is the pH of the intravenous solution? Does it cause irritation when it gets outside the vein? I believe there is seldom a great hurry in getting the drug into the patient. It is very wise to inquire whether the drug has been given at home before hospital entrance.

DR. BARNETT.—The pH of 1 per cent sodium sulfapyridine is 1.4. It causes marked reaction when it gets outside the vein.

DR. G. HEARN BRADLEY, NASHVILLE.—Is there any way of testing the patient's susceptibility to sulfapyridine before giving it?

CHAIRMAN SMITH.—I know of no way.

DR. JULIUS MARGOLIS, COATSVILLE, PA.—How about giving methylene blue by mouth?

DR. BARNETT.—If it is begun when the sulfapyridine is begun, methemoglobin will not accumulate; but, if a large amount of methemoglobin has been allowed to accumulate, it is more effective to administer methylene blue intravenously one time and to prevent reaccumulation by oral administration of the drug.

DR. MARGOLIS.—What is adequate dosage of methylene blue by mouth?

DR. BARNETT.—For patients weighing less than 20 kg., 1 gr. every 4 hours; over 20 kg, 2 gr. every 4 hours. Intravenously we give 0.1 to 0.2 c.c. of 1 per cent solution of methylene blue per kilogram.

DR. KENNEDY.—What do you call "poisoning"?

CHAIRMAN SMITH.—Unnecessary toxic symptoms, such as cyanosis, extreme restlessness, liver or kidney damage, effect on bone marrow. All of these effects are unnecessary.

DR. VIVIAN TAPPAN, TUCSON, ARIZ.—I would like to ask Dr. Smith about giving sulfapyridine to children with previous kidney damage.

CHAIRMAN SMITH.—It should be given very cautiously.

DR. BARNETT.—We have had one case. Small doses of the drug gave high blood concentrations.

DR. CULLEN.—The levels of the conjugated drug should be carefully watched.

DR. ALWIN C. RAMBAR, CHICAGO.—I would like to ask Dr. Smith his opinion of the value of sulfapyridine in otitis media accompanying pneumonia.

CHAIRMAN SMITH.—I have no figures on the incidence of otitis media in pneumonia, but it is very common. We gave all our babies in the ward sulfanilamide in the hope of preventing otitis, but we were unsuccessful.

DR. NORBERT D. GANNON, ERIE, PA.—Would you advise giving sulfapyridine prophylactically in respiratory diseases?

CHAIRMAN SMITH.—No. It should be reserved for serious diseases. It has not been proved to be of value in the common cold.

DR. LEWIS W. HILL, BOSTON.—Nothing has been said about the use of serum.

CHAIRMAN SMITH.—All patients should be typed, and if there is an effective serum for the type involved in a given case, it should be administered if the case is severe. However, the fact that effective sera are not available for all types and the great expense involved certainly make serum therapy less useful than chemotherapy. It costs $100 to treat a patient with serum and $1.50 for sulfapyridine.

DR. BROWN.—Do you give parenteral fluids for the general treatment of pneumonia?

CHAIRMAN SMITH.—You have to combat dehydration, and if it isn't possible to give sufficient fluids by mouth they can be given parenterally. Parenteral methods are sometimes used unnecessarily. I've seen a child drink a glass of water right after the completion of an intravenous injection.

DR. CULLEN.—We give 3 oz. of fluids per pound per day by any means possible.

DR. W. J. SIEMSON, CHICAGO.—Should sulfapyridine be given in all cases of lobar pneumonia?

CHAIRMAN SMITH.—Yes. Children do die of lobar pneumonia and its complications. It should be given, but I want to plead against giving it over longer periods than is necessary. It is a useful drug but it is also a potentially dangerous drug.

QUESTION.—How difficult is the microtechnique for blood concentration determination?

DR. BARNETT.—A photoelectric colorimeter is required. They are expensive, and a specially trained technician is required. The microtechnique requires 1 c.c. of blood and can be done in any laboratory doing blood chemistry.

DR. EPSTEIN.—Can the urine be tested for sulfapyridine?

DR. CULLEN.—Both sulfapyridine and sulfanilamide can be found in the urine, but this is not important. What we're interested in is the blood level.

REPORT OF THE COMMITTEE ON MENTAL HYGIENE

Plan for Teaching of Mental Hygiene

THE Committee on Mental Hygiene of the American Academy of Pediatrics would like to make the following comments regarding the teaching of mental hygiene in the medical schools and suggest a program for this teaching.

1. It is generally agreed that pediatrics concerns itself with growth and development of children. This definition implies a consideration of those factors which stimulate an optimum growth and development of each child, the problems of child rearing, and the care and general supervision of sick and well children.

2. The teaching of all phases of the subject to medical students, interns, and residents enables them to grasp the problems of the whole child and the child as a whole.

3. In teaching the fundamental principles of normal growth or health of children, the intellectual and emotional as well as its physical phases are considered. In addition, medical students can learn to analyze and evaluate the effect of environmental factors on the mental and physical health of children.

4. Because of the integral relationship between physical and mental growth and the physiologic influence of one upon the other, a consideration of mental health is an important part of every pediatric teaching program. This becomes more important when one realizes the importance of the first two years of life, which period is almost entirely under the care of a pediatrician, or general practitioner of medicine. During the first part of life, physical and mental growth cannot be easily distinguished from one another; the same reactions have physiologic and emotional attributes. Good physical hygiene is good mental hygiene and vice versa. Especially during infancy, mental health is dependent upon physical health and vice versa.

5. For these reasons, the Committee on Mental Hygiene would like to suggest to the chiefs of the departments of pediatrics of medical schools and hospitals the following plan of teaching.

I. A short series of lectures to first year medical students which will sensitize them, orient them, and awaken them to the tremendous importance of this phase of child care and its relation to practical medical practice.

II. A course in growth and development in the department of pediatrics which would bring out the interrelationship of physical and mental health.

III. A course in the department of pediatrics covering habits, management of emotional difficulties, attitudes and techniques of parents, social adjustment, adolescence, and the management of problems such as anorexia, enuresis, and school problems. This course should stress preventive technique. It should consider the signs of serious behavior problems in need of extreme psychiatric care.

IV. The mental hygiene aspect of the management of sick children should be integrated with bedside and clinic teaching. The well-baby clinic can be utilized to demonstrate normal growth and the psychologic as well as the physical care of normal babies.

V. It is felt that mental health can, partly at least, be taught by the pediatric staff or by those who speak and feel the pediatric idiom rather than by psychiatrists without pediatric training or experience. A pediatrician who has had training and experience in mental hygiene problems of children may be better able to present the subject to medical students than a psychiatrist who has not had extensive experience with children.

VI. A mental hygiene clinic in the departments of pediatrics has an invaluable influence on medical students and the pediatric staff. In this way every one can observe psychiatric technique and follow his own cases which are largely lost if referred to another department.

VII. Machinery can be set up in pediatric wards and hospitals for teaching interns and house officers.

In proposing this program, it is recognized that it is a matter for each school and hospital to work out a program in keeping with its facilities and methods of teaching.

Respectfully submitted,

Chairman, Dr. Bert I. Beverly

Dr. C. A. Aldrich
Dr. Frederick H. Allen
Dr. Horton Casparis
Dr. Bronson Crothers
Dr. George Mohr
Dr. Arthur H. Parmelee
Dr. Victor E. Stork

The above report has been approved by the Executive Board since the meeting in Cincinnati, as well as the following recommendations:

1. It is recommended that the name of the committee be changed to the Committee on Mental Health.

2. The committee suggests that the programs of the Academy should include more papers on mental health. They specifically suggest a panel discussion and at least one round table devoted to the subject at the next annual meeting. The committee will be glad to aid in any way in forming these programs.

3. The papers on mental health topics being published in THE JOURNAL OF PEDIATRICS are to be continued.

4. The Committee on Mental Hygiene will suggest to the Committee on Education that a copy of the suggested program for the teaching of mental hygiene in the medical schools be sent to the dean and the chief of the department of pediatrics of each medical school. We wish to emphasize that this program is suggested only; each medical school must, of necessity, work out its own program for teaching.

5. The Committee on Mental Hygiene feels that motion pictures, scientifically written and produced free of advertising, could do much to focus attention on the principles of mental health. The opinion was expressed that the committee should stimulate interest in the production of such pictures in a way commensurate with the policy of the Academy.

6. The committee will make recommendation on the management of adolescents in hospitals and clinics in the near future.

Academy News

The annual meeting of Region II, of the American Academy of Pediatrics, will be held at the Edgewater Gulf Hotel, at Edgewater Park, Miss., on *Friday and Saturday, March 15 and 16, 1940,* instead of March 22 and 23, as the dates originally selected conflict with the Easter holidays.

An interesting program has been prepared for the scientific session, and, in addition to clinical papers, round table and panel discussions have been planned. Opportunity will be afforded for delightful recreation on the Gulf Coast during its most attractive season. It is suggested that reservations be made immediately by writing directly to the hotel.

Dr. D. Murray Cowie, Ann Arbor, Mich., died suddenly on Jan. 27, 1940. Dr. Cowie, professor of pediatrics at the University of Michigan School of Medicine, was one of the founding members of the American Academy of Pediatrics.

Dr. S. W. Clausen has been added to the Committee on Vitamins.

Dr. Adolph G. DeSanctis has accepted appointment on the Committee on Postgraduate Education.

Errata

In the article, "Vitamin A Requirements in Infancy as Determined by Dark Adaptation," by J. M. Lewis, M.D., and C. Haig, Ph.D., which appeared in the December, 1939, issue of the Journal, two errors occurred on page 821: In lines 20 and 26 the phrase "6 to 8 mg. of vitamin A" should be changed to read "6 to 8 micrograms of vitamin A" instead.